FORMULATION AND EVALUATION OF ORALLY DISINTEGRATING TABLET OF TASTE MASKED DRUG

A dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of Degree of

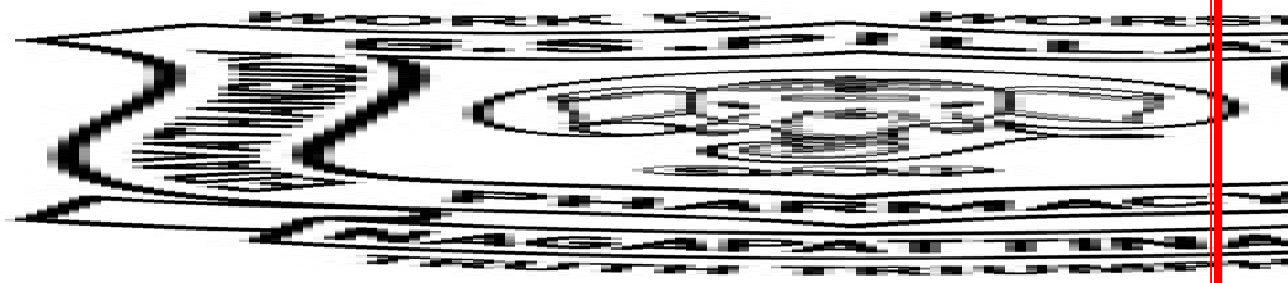
MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted
By

Reg No: 261211153



DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

NAGAPATTINAM-611002

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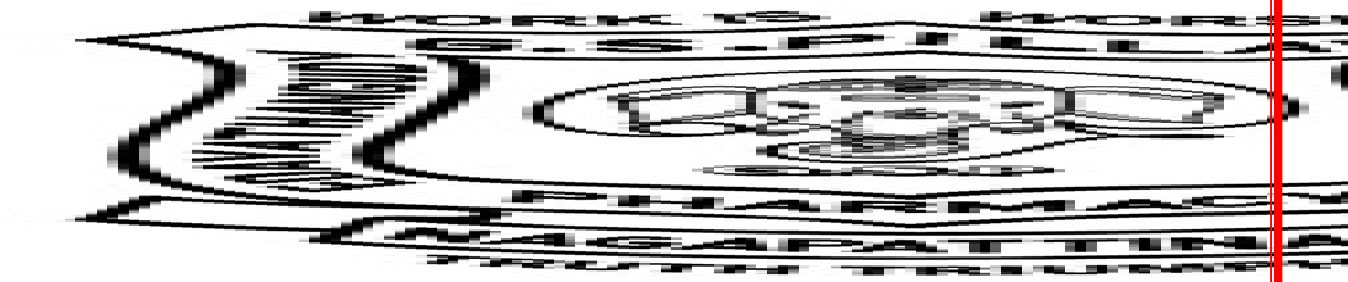
Under the guidance of

Prof.Dr.M.Murugan, M.Pharm., Ph.D.,



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CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF ORALLY DISINTEGRATING TABLET OF TASTE MASKED DRUG"** submitted by **RBRIGHT LAZAR RAJA** (Reg No:261211153) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under my guidance in the Department of Pharmaceutics, Edayathangudy.G.S.Pillay College of Pharmacy during the academic year 2013-2014.

Place: Nagapattinam **Prof.Dr.M.Murugan, M.Pharm., Ph.D.,**

Date:

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CONTENTS

INTRODUCTION

1. Definition of ODT: [1]

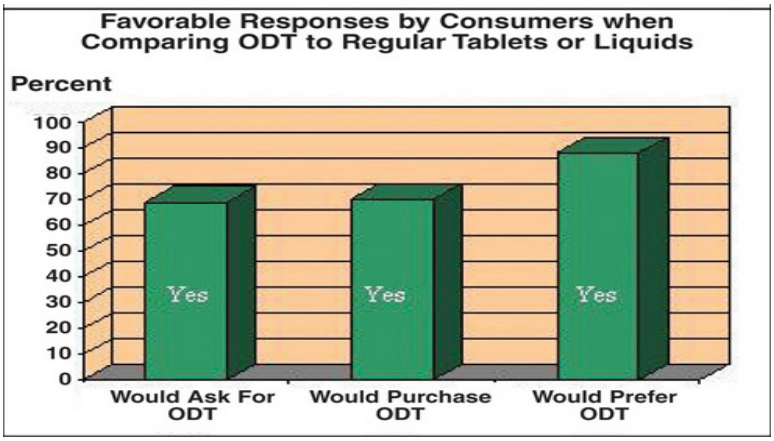
Generally, an ODT is a solid-dosage form that disintegrates and dissolves in the mouth (either on or beneath the tongue or in the buccal cavity) without water within 60 seconds or less. The US Food and Drug Administration's Center for Drug Evaluation and Research developed the following definition for an *ODT* as a new dosage form in 1998: "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"

FDA issued draft guidance, *Guidance for Industry: Orally Disintegrating Tablets,* to recommend that, in addition to the original definition, ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity with an *in vitro* disintegration time of approximately 30 s or less, when based on the United States Pharmacopoeia disintegration test method or alternative. [2]

2. Market potential: [3]

Recent market studies indicate that more than half of the patient population prefers ODT to other dosage forms, and most consumers would ask their doctors for ODT (70%), purchase ODT (70%), or prefer ODT to regular tablets or liquids (greater than 80%) [1]

Fig-1: Consumer's preference of choosing ODT



The global ODT market was estimated at $2.4 billion in 2004 and $3 billion in 2006, according to Technology Catalysts International

Recently, increasing numbers of active pharmaceutical ingredients (APIs) have been formulated into orally disintegrating dosage forms. The current market consists of more than 145 launched products (both branded and generic) for 92 molecules (and combinations), which is an increase of 10 molecules and more than 15 brands from 2004, including prescription and over-the-counter (OTC) segments. ODT therapies for central nervous system disorders (depression, mood disorders, migraine headaches, Alzheimer's disease, insomnia, anxiety) still dominate the market, accounting for more than 40% of the market value. Gastrointestinal (GI) ODTs increased in share to 34% by value, oncology to 10%, and diabetes to 7%. In 2005–2006, brand companies learned that patients perceived a faster onset of action with an ODT, and caregivers welcomed the ease of administration of ODTs to patients who are reluctant to comply with medical orders or who became combatant when administered their medicine. These are likely the contributing factors to the high growth in the ODT market [(4)]

3. Advantages:

- Hard tablets, not fragile and easy to handle.
- No specific packaging required, can be packaged in push through blisters.
- Smooth mouth feel and pleasant taste.
- Conventional manufacturing equipment, not difficult to transfer to final production site.
- Cost effective.

4. Types of ODTs:

For ease of comparison, ODT may be categorized into two main groups: lyophilized formulations and loosely compressed tablets. Thin-film strips form a third category of

solid, unit-dose, orally disintegrating products that aim to meet the same objectives of ease of administration, patient convenience, and improved compliance.

5. Challenges to Develop ODT:

Taste:

There are numerous pharmaceuticals that contain actives, which are bitter in taste. With respect to OTC preparations, such as cough and cold syrups, the bitterness of the preparation leads to lack of patient compliance. The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. In order to ensure patient compliance bitterness masking becomes essential. Molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. This sensation is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste.

Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor. An ideal taste masking process and formulation should have the following properties.[5]

Techniques Employed for Taste Masking:

- **Taste masking with Flavor enhancer:**[6]

Flavoring and perfuming agents can be obtained from either natural or synthetic sources. Natural products include fruit juices, aromatic oils such as peppermint and lemon oils, herbs, spices and distilled fractions of these. They are available as concentrated extracts, alcoholic or aqueous solutions, syrups or spirit. Apart from

these conventional materials many compositions have been found to show effective taste masking abilities with improved flavor such as alkaline earth oxide, alkaline earth hydroxide or an alkaline hydroxide. Another composition includes phosphorylated amino acid such as phosphotyrosine, phosphoserine, and phosphothreonine and mixtures thereof. Anethole effectively masked bitter taste as well as the aftertaste of zinc. Clove oil and calcium carbonate, which has been found to be particularly useful to mask the unpalatable active in formulations which are intended to be chewed or dissolve in mouth prior to ingestion in solution.

- **Taste masking with lipophilic vehicles:** [7]

Lipids: Oils, surfactants**,** polyalcohols, and lipids can be used for taste masking of bitter drugs. These substances act as taste masking agents by increasing the viscosity in the mouth and coat the taste buds. Carnauba wax, magnesium aluminium silicate, glyceryl monostearate, gelatin, partially hydrogenated soyabean oil, polyglycerine, fatty acid esters, chained triglycerides.

Lecithine and Lecithine like Substances: Addition of sufficient amount of lecithine and licithne like substances can completely mask the bitter taste of drugs. Taste masked composition is prepared by dissolving or dispersing the bitter active into a suitable organic solution followed by addition of lecithine to mask a blend and finally granulating the blend with other excipients to prepare a taste masked grasnules. Soyabean lecithine, homogenated suspensions of phosphatidic acid and beta lacto globuline from soyabean and milk respectively.

- **Taste masking by Coating with Hydrophilic vehicles:** This is the simplest and most feasible option to achieve taste masking. Coating prevents the interaction between drug molecules and taste buds.

Carbohydrates: Coating the drugs with polymeric membrane can mask the taste of orally administered bitter drugs. Bitter solid drugs are formulated in an organoleptically acceptable manner by particle coating with a mixture of a water

insoluble film forming polymer and second film forming polymer soluble at pH less than five. Example is bitter solid drug such as pinaverium bromide.

Adsorption onto the polymeric carbohydrates is an effective for reducing the bitter taste of active ingredients. Taste masking of ibuprofen has been successfully achieved by using air-suspension coating techniques to form microcapsules, which comprise a pharmaceutical core of crystalline ibuprofen and a Methacrylic acid Co-polymer [Eudragit] coating that chewable taste–masked characteristics.
Chlorpheniramine maleate can be adsorbed onto Avicel PH 101 porous particles as an aqueous solution containing 50 parts Chlorpheniramine maleate onto 3000 parts of the polymeric material. The product obtained after adsorption was spray coated with an aqueous solution containing xylitol to get the final coated product that was tasted masked. The compressible grade formulation of xylitol is available as Xylitab.Triprolidine hydrochloride was taste masked with dispersion coating of water-soluble polymer hydroxypropyl cellulose, plasticizing agent, and sweetener and flavoring agent.

Pharmaceutical granules with bitter taste are coated with water- soluble polymers of hydroxypropyl methyl cellulose and sugars such as sucrose and lactase to decrease the bitter perception at the time of administration .The bitter taste of basic pharmaceutical salts can be reduced or masked with weakly alkaline compounds of good bioavailability

Proteins, Gelatins and Prolamines: Prolamine, an important protein component can mask the taste of bitter active pharmaceuticals. Important prolamines used for taste masking are Zein, Gliadin and Hardein. Advantages of using prolamines as taste masking agents are as follow

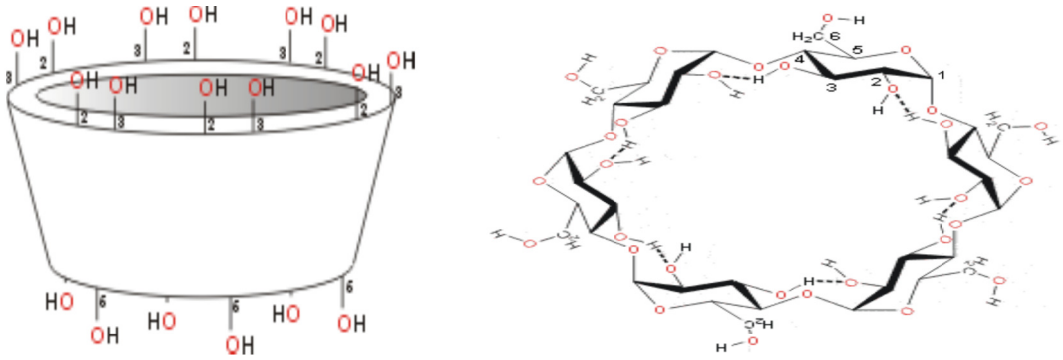
- **a.** Stability of tasrte masking effect during a long term storage period.
- **b.** No interference with the immediate bioavailability of the drug.
- **c.** In combination with the plasticizer, prolamine can controll the release of the drug without any -harmful effect to taste masking.

Gelatins: Hydrolyzed gelatin has been found to provide an improvement in taste and mouth feel when incorporated into small amounts in chewable tablets containing ingredients for taste masking. Water insoluble gels formed by Sodium alginate in the presence of bivalent metals are also exploited for their taste masking properties. Amiprilose HCl was taste masked by first coating the drug with calcium gluconate followed by a coating of sodium alginate.

- **Taste masking by drug-beta cyclodextrin inclusion complexation:** [8]

Cyclodextrins are non-reducing cyclic glucose oligosaccharides resulting from the cyclomaltodextrin glucanotransferase catalyzed degradation of starch. Their structures have been reviewed. There are three common cyclodextrins with 6, 7 or 8 D-glucopyranonsyl residues (α-, β-, and γ-cyclodextrin respectively) linked by α-1,4 glycosidic bonds. The glucose residues have the $^4C_1$ (chair) conformation. All three cyclodextrins have similar structures (that is, bond lengths and orientations) apart from the structural necessities of accommodating a different number of glucose residues. They present a bottomless bowl-shaped (truncated cone) molecule stiffened by hydrogen bonding between the 3-OH and 2-OH groups around the outer rim. The hydrogen bond strengths are α-cyclodextrin < β-cyclodextrin < γ-cyclodextrin. The flexible 6-OH hydroxyl groups are also capable of forming linking hydrogen bonds around the bottom rim but these are destabilized by dipolar effects, easily dissociated in aqueous solution and not normally found in cyclodextrin crystals. The hydrogen bonding is all 3-OH (donor) and 2-OH (acceptor) in α-cyclodextrin but flips between this and all 3-OH (acceptor) and 2-OH (donor) in β- and γ-cyclodextrins.

Fig-2 Molecular structure of Cyclodextrin:



The cavities have different diameters dependent on the number of glucose units (empty diameters between anomeric oxygen atoms given in the diagram below). The side rim depth (shown below in the diagrams) is the same for all three (at about 0.8 nm).Cyclodextrin rings are amphipathic with the wider rim displaying the 2- and 3-OH groups and the narrower rim displaying 6-OH group on its flexible arm. These hydrophilic groups are on the outside of the molecular cavity whereas the inner surface is hydrophobic lined with the ether-like anomeric oxygen atoms and the C3-H and C5-H hydrogen atoms. In aqueous solution, this hydrophobic cavity contains about 3 (α-DC), 7 (β-DC) or 9 (γ-DC) poorly held (but low entropy) and easily displaceable water molecules. This water in the cavities has low density as the cavities are large enough to accommodate several more molecules. Thus, the otherwise hydrophilic cyclodextrin molecules may bind non-polar suitably-sized aliphatic and aromatic compounds such as aroma compounds and lipophilic drugs. They may bind in 1:1, 2:1 and 1:2 ratios dependent on the molecules involved. The binding is driven by the enthalpic and entropic gain on the reduction in the hydrophobe-aqueous surface and the release of water molecules from the cavity to the bulk phase. Such binding also allows cyclodextrins to be used to increase the water solubility of normally hydrophobic compounds or minimize undesirable properties such as odor or taste in certain food additives.

Fig-3: General and 3-D structures of 3 types of cyclodextrins:

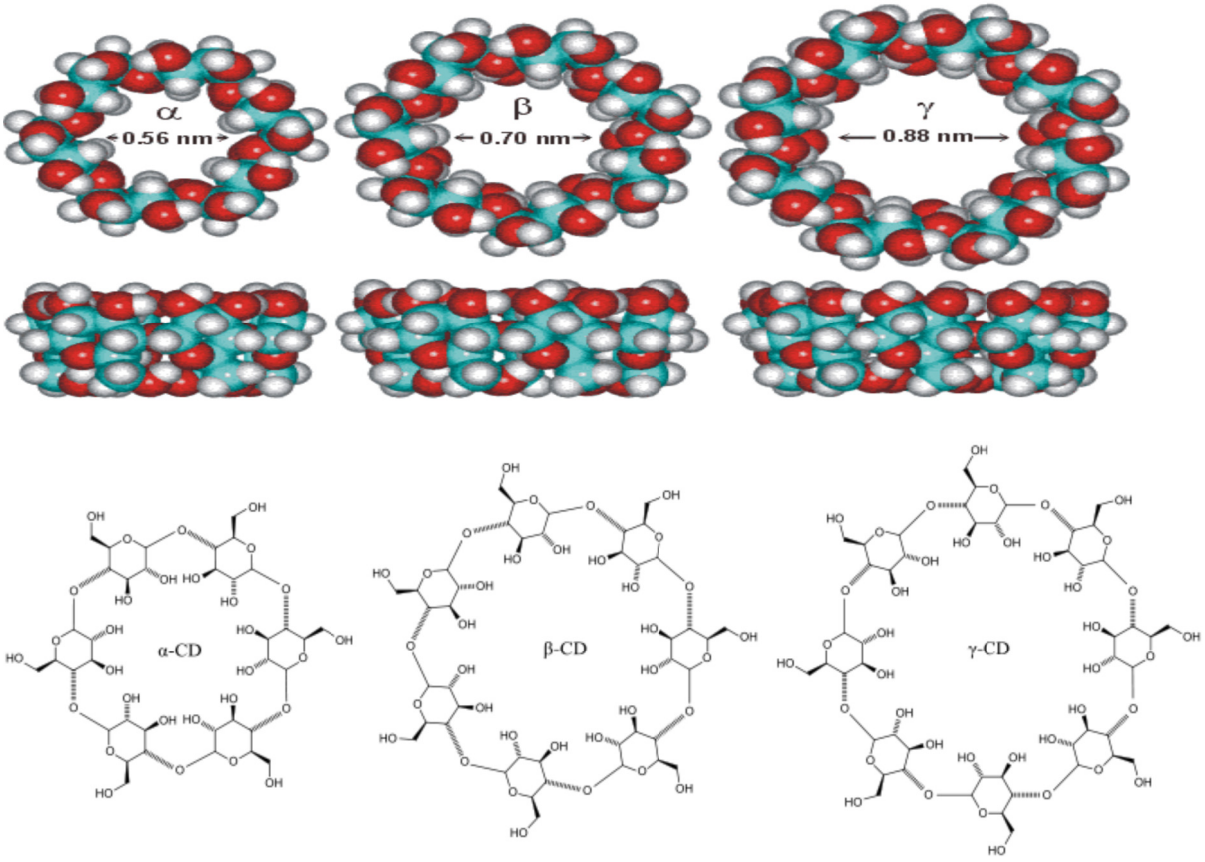


Table-1: Comparison of properties of three types of cyclodextrins.

Properties of cyclodextrins							
Cyclodextrin	**Mass**	**Outer diameter, (nm**	**Cavity diameter (nm)**		**Solubility, g/kg H_2O**	**Hydrate H_2O**	
			Inner rim	Outer rim		cavity	external
α,(glucose)$_6$	972	1.52	0.45	0.53	129.5	2.0	4.4
β,(glucose)$_7$	1134	1.66	0.60	0.65	18.4	6.0	3.6
γ,(glucose)$_8$	1296	1.77	0.75	0.85	249.2	8.8	5.4

Mechanism of Complex formation: [9] Crystalline beta cyclodextrin contains 13-14% (w/w) water. Half of this water is so called crystal water and other half is inclusion water. The crystal water is located and bound between the adjacent CD molecules, while the

inclusion water is included into the hydrophobic cavity of the CD. The mechanism of complex formation is always the substitution of these water molecules by a more appropriate, more hydrophobic guest molecule, which forms a more stable complex with the CD.

Method of complex formation:

- **Kneading:** Weigh required quantity of drug and CD and take in a mortar. Start kneading with pestle with slowly addition of water for some time and kept it for drying at 45˚C. The dried complex was kept in a well closed container after passing through mesh# 60.
- **Co-Crystallization:** Required amount of drug is dissolved in required amount of warm or cold solvent and mixed with suspension of β CD in water. This mixture is stirred and heated until complete dissolution of the β CD. After standing for sufficient time a precipitation of a white microcrystalline complex occurred that can be isolated by filtration.
- **Spray drying:** Mix the drug and CD in appropriate ratio and dissolve the mixture in required amount of water and heat the aqueous mixture to 80˚C till complete dissolution then spray dried to a non bitter powder.

Taste masking by ion-exchange resins: [10]

Ion exchange resin may be defined as high molecular weight water insoluble polymers containing fixed positively or negatively charged functional groups in their matrix which have an affinity for oppositely charged counter ions. Since the majority of drugs posses an ionic site in their molecules the charge of the resin provides a means to loosely attach such drugs to insoluble polymers. The principle property of these resins is their capacity to exchange bound or insoluble ions with those in solution. Soluble ions

may be removed from solution through exchange with the counter ions absorbed on the resin. These exchanges are equilibrium reaction in which the extent of exchange will be governed by the relative affinity of the resin for particular ions.

Physical properties and chemistry of IER: [11] In general IER consists of spherical beads of approximately 0.5-1.2 mm in diameter. The most common type is an opaque yellow in color, although other colors are also reported. The construction of each spherical particle of IER is similar to that of a homogeneous gel. The shrinkage or expansion of the spherical volume that take place is based on the ionic environment in which the IER is present. The insolubility of IER depends upon the nature of the counter ion and the extent of cross linking of the basic skeleton of IER and hence careful consideration should be given to the selection of IER. Commercially available IER swell in water to 2-3 times their original weight. Despite strong swelling, the chemical stability remains satisfactory.

Chemically IER are made up of two components: a structural component consisting of the polymer matrix, and a functional component to which the counter ion in bound. The structural component of IER consists of a stable acrylic polymer of styrene- divinylbenzene copolymer, whereas the functional component can be acidic (sulfonic and carboxylic) or basic (amine)

Types of Ion Exchange Resins: [12]

Cation exchangers (Anionic resin):

Cation-exchange resin is prepared by the copolymerization of styrene and divinyl benzene and have sulphonic acid groups ($-SO_3H$) introduced into most of benzene rings.

The functional groups of these resins undergo reaction (exchange) with the cations in the surrounding medium.

The mechanism of cation exchange can be depicted by the following reaction.

$Resin^- - ex^+ + C^+ \rightarrow Resin^- - C^+ + ex^+$

Where, $Resin^-$ indicates polymer with SO_3^- sites available for bonding with exchangeable cation (ex^+) and C^+ indicates cation in the surrounding solution getting exchanged. Cation exchangers are again subdivided into inorganic and organic. Inorganic includes two classes i.e. Natural (e.g. modified green sand, clays) and Synthetic (e.g. zeolite). Organic ion exchangers are subdivided into 3 groups. Natural (peat, ignite), Semisynthetic (Sephadex ion exchangers, zeocrab), Synthetic (acrylic acid copolymers)

Anion exchangers (Cationic resin)

These are the polyelectrolytes undergoing reaction with the anions of the surrounding solutions. They are prepared by first chlor-meythylating the benzene rings of styrene-divinylbenzene copolymer to attach CH_2Cl groups and then causing these to react with tertiary amine such as triethylamine. The mechanism of anion exchange can be depicted by the following reaction.

$Resin^+ - ex^{-+} A^- \rightarrow Resin^+ - A^- + ex^-$ (2)

Where, $Resin^+$ indicates polymer with N^+ sites available for bonding with exchangeable anion ($ex^{-)}$ and A^- indicates cation in the surrounding solution getting exchanged.

Advantages of resins

- Resins being polyelectrolyte have extensive binding sites leading to very high drug loading ability.
- They are chemically inert and free from local and systemic side effects.

- Because of ion exchange ability, they have been used in taste masking, modified release and therapeutic applications.

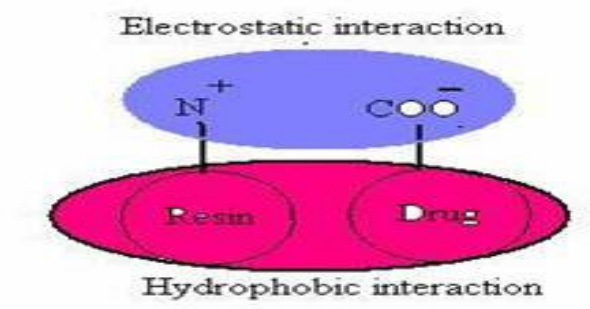
- All conventional solid, semisolid and liquid dosage forms can be prepared by using resins.

- They have been used in selective separation/recovery of pharmaceuticals from mixtures.

- Being stable to all sterilization means, can be formulated in to all sterile dosage forms.

Types of Drug Resin Interactions:

Fig-4: Electrostatic and hydrophobic interaction seen in drug resin complex**.**



The chemistry of resinate is such that the drug retains its characteristics but is immobilized on a solid support. The interactions between the IER and drug although primarily chemical in nature, are also partially a result of physical adsorption. These interactions are commonly referred to as adsorption on IER. The IE process therefore is generally regarded as a double –decomposition process, in which the IER used are able to provide the type of ion required to replace the one that is adsorbed from the solution the ion of the IER, which can be exchanged for a drug counterpart, is called a counter ion. The affinity of counter and drug ions towards the IER is competitive.

Factors Affecting Resin Performance:

- **Degree of cross linking:** Less degree of cross linking results more porous resin which exhibit higher extent of swelling due to hydration. Whereas, if it is less cross linked, then it has less swelling. Because of this, the drug loading ability of less cross linked resin is high than more cross linked. But, the drug release from former is rapid and sustained from latter ones.
- **Particle size:** The smaller resin beads offering more surface area have shown rapid exchange of ions but shorter diffusion path length. Whereas, the larger beads, have more diffusion path length leading to sustained release**.**

- **pH:** If the pH of surrounding medium is acidic then it promotes dissociation of basic drugs leading to formation of more ionic species available for drug loading. And towards alkaline pH, the dissociation of acidic drugs will be promoted. With increase in dissociation, the complexation efficiency gets improved. With increase in pH, protonated fraction of cationic drug decreases and hence interaction with resin or loading with beads decreases. It has been observed that, release of phenylpropanolamine was rapid in eluants with low pH.

- **Size of exchanging ion:** It has been observed that, with increase in size of exchanging ion, slower was drug loading, and less diffusion rate followed by slow release.

- **Selectivity of counter ion:** The ions with low selectivity for resin such as $-H^+$ get replaced faster by cationic drugs resulting in higher loading.

- **Mixing time:** With increase in the mixing time, the swelling of resin goes on increasing and ultimately drug loading. In the initial phases, the drug loading seen was more and later on it was less. It has been reported that, complete drug loading can be achieved in 1-2 hour only by batch process.

- **Effect of temperature:** For certain resins the effect of temperature on drug loading has been reported. High temperature may also cause swelling of resin. Cation exchange resin does not get significantly affected by temperature changes unlike anion exchangers.

- **pKa:** The pKa value of the resin is having significant influence on the rate at which the drug is released from the resinate in the gastric fluids. The anionic resins having sulfonic, phosphoric or carboxylic acid exchange groups have approximate pKa values of <1-6. And, cationic resins containing quaternary, tertiary, or secondary ammonium groups have pKa values of 5-13 and greater than 13.The pKa of drug also decides the extent of dissociation and complexation with the resin.

- **Ion exchange capacity:** The IE capacity of strong ion exchange resin is determined as meq/gm by evaluating the number of moles of Na^+ which are absorbed by 1 gm of the dry resin in the hydrogen form. Similarly the IE capacity of a strong basic AER is evaluated by measuring the amount of Cl^- taken up by 1 gm of the dry resin in the hydroxide form.

Preparation of Resinate:

- **Batch technique:** In this processs a specific quantity of the granular IER is agitated with drug solution until the equilibrium is achieved.
- **Column technique:** A concentrated solution of drug is passed through the IER packed column until the effluent concentration is the same as the eluent concentration.

Miscellaneous taste Masking Approaches: [7]

- **By effervescent Agent:** Taste masking of bitter actives for oral delivery can be achieved by adding required quantity of effervescent agents in the formulation. In addition to the effervescent agents taste masking generator of carbon dioxide and a taste bud desensitizing agent is also incorporated. Recently taste masked formulation of Fentanyl and Prochlorperazine with effervescent agents have been developed.
- **Rheological Modifications**: Rheological modifiers play an important role for taste masking of pharmaceutical liquid preparation. These agents prevent the diffusion of bitter active substances from the saliva to the taste buds. Examples include xanthan gum, microcrystalline cellulose, PEG, PPG with polyvinyl pyrollidone, gum arabic, gelatin, sodium alginate, maltitol. Drugs like Acetaminophen, Phenobarbital, Tannic acid and Mitrazapine have been successfully taste masked by this process.

- **Salt preparation:** Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of drugs. Caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acids, citric acid and tartaric acid.

- **Solid Dispersion Systems:** Solid dispersion has been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method. Solid dispersion is also called as co precipitates for those preparation obtained by solvent method such as co precipitates of sulphathiazale and povidone. Solid dispersions using insoluble matrices or bland matrices may be used to mask the bitter taste of drugs. Also

using them as absorbates on various carriers may increase the stability of certain drugs.

2. Mouth feel: [13]

Mouth feel is critical and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.

3. Disintegration Time:

The time for an ODT to disintegrate in the oral cavity also varies by product and the method of manufacturing. Compressed tablets will typically take slightly longer to disintegrate than freeze-dried wafers due to a different bonding mechanism and differences in porosity between the two dosage forms. Compression-molded tablets would be expected to have disintegration times that are similar to compressed tablets. The method used to determine disintegration time is also critical, and the disintegration method stated in the United States Pharmacopoeia (USP) for conventional "hard" tablets may not be appropriate. USP 26 states that method is: "provided to determine compliance with the limits on disintegration stated in the individual monographs except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed."

The lack of an appropriate disintegration test for ODT products results in USP method being the only official method available. However, this test is quite aggressive for ODT products and results in disintegration times as short as a few seconds. Several companies have developed their own internal, more discriminating method to measure disintegration times of these dosage forms. In vivo disintegration times will vary tremendously depending on how the patient processes the dosage form. A patient that actively moves the product around the oral cavity with the tongue will experience a faster disintegration time than one who allows the product to disintegrate without any additional

encouragement. It is important to note that even though this type of dosage form has inherent patient-to-patient disintegration time variability, an approved ODT must still meet the typical requirements for bioequivalence, independent of disintegration time.

4 .Dissolution Studies:

For bioequivalent formulation, USP monographs dissolution conditions should be followed in addition 0.1N hydrochloric acid, and pH4.5 and 6.8 buffers should be evaluated for orally disintegrating tablets. The USPII (paddle speed of 50rpm) apparatus is most suitable for ODT. For tablet weight one gram or more then paddle speed to be increased. The taste-masking plays major role in dissolution method development. Several companies are developing their internal standards to get more discrimination of the product performance.

5. Bioequivalace: [13]

Creating an ODT form of an existing immediate-release product means that the two formulations must be bioequivalent. This can be challenging, especially if the method of taste masking retards the dissolution rate of the active ingredient after disintegration of the ODT. Contrary to some patients' perceptions, shorter disintegration times do not necessarily mean quicker absorption. Typically, depending on the regulatory strategy, the pharmaceutical company wants to see drug dissolution rates for an ODT that are similar to the immediate-release innovator, at least until an IVIVC can be made. ODT formulations are designed to disintegrate quicker than their counterparts, and this can lead to difficulties finding a discriminating dissolution test method. If, for example, 90% of the drug is released in 5 minutes, any small batch-to-batch changes may be difficult to identify.

1. **M.E. Bhanoji Rao, K.E.V. Nagoji, G. Chandrasekhar** prepared and evaluated dispersible tablets of nimesulide using primojel as dispersing agent with starch, lactose and dicalcium phosphate as diluent. The formulation with starch and lactose as diluent showed fast and rapid dissolution when compared to that of commertial tablets where as formulatons with dicalcium phosphate as diluent showed less dissolution rate. [(25)]
2. **Sarath Chandar, Gary Telfer Norman, Kalyan S. Nuguru, Arun F. Amin** disclosed a co-processed carbohydrate system as a quick- dissolve matrix for solid dosage forms in US patent no US 7,118,765 B2. They invented a directly compressible quick dissolve matrix prepared by spray dried Mannitol and sorbitol followed by addition of superdisintegrants for achieving invivo disintegration time of less than 60 seconds and lubricant for good flow property. [(24)]
3. **Kiran Bhise,Shafi Shaikh,and Divyakumar Bora** masked the bitter taste of Diphenhydramine Hydrochloride (DPH) using cation exchange resins Indion 234 and Tulsion 343 .The drug resin complexes (DRC) were prepared by batch process by taking drug: resin ratios 1:1, 1:2, and 1:3. Effervescent and dispersible tablets were developed from optimum drug: resin ratios of 1:2 and 1:1. The formulations were evaluated for uniformity of dispersion, disintegration time, and in vitro dissolution.. The drug release of 95% in 15 min was observed for effervescent and dispersible tablets.[(26)]
4. **A. S Mundada, D.R Meshram, H. B Banbale, M. R Bhalekar, J. G Avari** masked the bitter taste of roxithromycin by complexation technique. Weak cation exchange resins Indion 214 and Amberlite IRP64, polymer carbopol 934P were used in formulation of complexes with the drug. The loading process was optimized for the pH of loading solution and resin or polymer:drug ratio. The complexes were evaluated for bulk density, angle of repose, taste masking, and *in vitro* drug release. *In vitro* drug release studies showed more than 80% drug release from the optimized formulation within 30 min. Amberlite IRP64 was found to be better complexing agent for masking the bitter taste of roxithromycin. [(27)]

5. **Shagufta Khan, Prashant Kataria, Premchand Nakhat, and Pramod Yeole** performed taste masking by complexing ondansetron HCl with aminoalkyl methacrylate copolymer (Eudragit EPO) in different ratios by the precipitation merethod. Polyplasdone XL-10 7% wt/wt gave the minimum disintegration time. Tablets containing spray-dried mannitol and microcrystalline cellulose in the ratio 1:1 and 7% wt/wt Polyplasdone XL-10 showed faster disintegration, within 12.5 seconds, than the marketed tablet (112 seconds).Tablets revealed rapid drug release (t_{90}, 60 seconds) in SGF compared with marketed formulation (t_{90}, 240 seconds;). Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity. [28]
6. **Punit P. Shah and Rajashree C. Mashru** masked the intensely bitter taste of amotidineArtemether and formulated a rapid-disintegrating tablet of the taste-masked drug. Taste masking was done by solid dispersion with mono amino glycyrrhyzinate pentahydrate by solvent evaporation method. To characterize and formulate taste masked rapid disintegrating tablets of ARM, the 1:1M solid dispersion was selected based on bitterness score. In vitro drug release studies were performed for RDTs at pH 1.2 and 6.8. RDTs prepared using solid dispersion, (RDT3), showed faster disintegration (within 28 s) and complete bitter taste masking of ARM. In addition, RDT3 exhibited better dissolution profile at both pH 1.2 and 6.8, than RDTs prepared from pure ARM (RDT5).[29]
7. **V. Ananda, R. Kandarapub, S. Gargc** prepared taste-masked orally disintegrating tablets of Prednisolone by incorporation of microspheres by the solvent evaporation method using acetone as solvent for pH-sensitive polymer and light liquid paraffin as the encapsulating medium. Taste evaluation studies confirmed that microspheres of PDL having a drug to polymer ratio of 1: 10 are tasteless and these were further used for formulation into ODTs. Compression of microspheres resulted in breaking of a fraction of the microspheres but this did not adversely affect the taste. Effective taste-masking was achieved for PDL using the technique of microencapsulation and ODTs of acceptable characteristics were obtained by disintegrants addition and direct compression.[30]

8. **Jianchen Xua, Li Li Bovetb, Kang Zhao** produced microspheres by spray drying a mixture of Famotidine with taste masking material and form orally disintegrating tablets. Results from an evaluation by a panel of six human volunteers demonstrated that the orally disintegrating tablets with taste masking microspheres improved the taste significantly.The taste masking potential of the microspheres incorporated in ODTs was evaluated by dissolution test of microsphere particles and tablets, *in vivo* rat study, and taste masking test as well as the disintegration time in the buccal cavity with a panel of human volunteers. The ODTs can disintegrate in the buccal cavity within 30 s with improved taste. The microspheres neither decrease the bioavailability nor delay the release of famotidine significantly.[31]
9. **Sambhaji Pisal, Rana Zainnuddin, Pradeep Nalawade, Kakasaheb Mahadik and Shivajirao Kadam** formulated tasteless complexes of ciprofloxacin with Indion 234 and evaluated molecular properties of drug complexes. The efficient drug loading was evident in batch process using activated Indion 234 with a drug-resin ratio of 1:1.3. Drug complexation enhanced with pH from 1.2 to 6, while temperature did not affect the complexation process. Infrared spectroscopy revealed complexation of –NH (drug) with Indion 234. DRC are amorphous in nature. Drug release from DRC in salivary pH was insufficient to impart bitter taste. Volunteers rated the complex as tasteless and agreeable. Complete drug release was observed at gastric pH in 2 hours. [32]
10. **Hiroyuki Suzuki , Hiraku Onishi, Yuri Takahashi , Masanori Iwata, Yoshiharu Machida** developed taste masked Acetaminophen oral chewable tablet using some matrix bases like Corn starch/lactose, cacao butter and hard fat (Witepsol H-15) and corrigents like sucrose, cocoa powder and commercial bitter masking powder mixture made from lecithin (Benecoat BMI-40). The present studies revealed that when the acetaminophen chewable tablets are made of various formulations, Witepsol H-15 containing Benecoat BMI-40 (5%)/sucrose (1 or 5%), or cocoa powder (1%)/sucrose (1%), or sucrose (5%) alone could mask bitter taste of the drug most excellently. Such masking effect appeared to be fairly related to lipophilic characteristics of the additives. Further, the tablets obtained

with the above formulations showed a good drug release in vitro irrespective of chewing. Thus, these tablets are proposed to be available as chewable acetaminophen tablets with inhibited bitter taste. However, Witepsol H-15 can cause an unpleasant feeling in the oral cavity because of its melting characteristics in the mouth, as expressed by volunteers. [33]

11. **C Mallikarjuna Setty, D.V.K Prasad, V.R.M Gupta, B. Sa** developed fast dispersible Aceclofenac tablets and studied the effect of functionality of superdisintegrants. Aceclofenac fast-dispersible tablets were prepared by direct compression method. Effect of superdisintegrants (such as, croscarmellose sodium, sodium starch glycolate and crospovidone) on wetting time, disintegration time, drug content, *in vitro* release and stability parameters has been studied. Disintegration time and dissolution parameters ($t_{50\%}$ and $t_{80\%}$) decreased with increase in the level of croscarmellose sodium. Where as, disintegration time and dissolution parameters increased with increase in the level of sodium starch glycolate in tablets. However, the disintegration time values did not reflect in the dissolution parameter values of crospovidone tablets and release was dependent on the aggregate size in the dissolution medium. Stability studies indicated that tablets containing superdisintegrants were sensitive to high humidity conditions. It is concluded that fast-dispersible Aceclofenac tablets could be prepared by direct compression using superdisintegrants. [34]
12. **J. Balasubramaniam, K. Bindu, V. U. Rao, D. Ray, R. Haldar and A. W. Brzeczko** studied the effects of selected superdisintegrants on the dissolution behavior of several cationic drugs with varying water solubility. All formulations were made with fixed disintegrant concentration and equal drug load using a model formulation. Tablets were made by direct compression and were compressed to equal hardness. Dissolution studies were carried out in dissolution media specified in the compendium (*USP*) or in media recommended by the U.S. Food and Drug Administration (FDA) for the respective actives. The effect of media pH on the dissolution of drugs was also evaluated. The use of crospovidone significantly improved the dissolution of the cationic drugs in the model formulation when compared with the other superdisintegrants studied.

Crospovidone can be effectively used as a tablet disintegrant to improve the dissolution of either soluble or poorly soluble cationic drugs. [35]

13. **Garala Kevin C., Ekshinge Vinit B., Jarag Ravindra J. and Shinde Anil J.** made an attempt had been made to prepare fast disintegrating tablets of the drug using different super disintegrants following wet granulation method. The sodium starch glycolate, cross carmellose sodium and pregelatinized starch (Starch 1500) were used in different concentrations according to the simplex lattice design as the super disintegrants. The tablets were evaluated for diameter, thickness, hardness, friability, weight variation, wetting time, percentage of water absorption, disintegration time and *in vitro* dissolution studies. The disintegration time of all formulation showed less than 89 seconds. Formulation containing equal amount of Cross carmellose sodium and pregelatinized starch showed fastest disintegration than other formulations containing Starch 1500, cross carmellose sodium and sodium starch glycolate in various proportions and the percentage drug release was 99.5 within 10 minutes.[36]

14. **S Furtado, R Deveswaran, S Bharath, BV Basavaraj, S Abraham and V Madhavan** investigated the effect of camphor as a subliming agent on the mouth dissolving property of famotidine tablets. Orodispersible tablets of famotidine were prepared using camphor as subliming agent and sodium starch glycollate together with crosscarmellose sodium as superdisintegrants. The formulations were evaluatedtidine for weight variation, hardness, friability, drug content, wetting time, in vitro and in-vivo dispersion, mouth feel and in vitro dissolution.All the formulations showed low weight variation with dispersion time less than 30 seconds and rapid in vitro dissolution. The results revealed that the tablets containing subliming agent had a good dissolution profile. The drug content of all the formulations was within the acceptable limits of the United States Pharmacopoeia XXVII. The optimized formulation showed good release profile with maximum drug being released at all time intervals.[37]
15. Formulation and characterization of fast-dissolving tablet of promethazine theoclate. **Shailesh Sharma, GD Gupta** prepared fast-dissolving tablets (FDT) of

promethazine theoclate by direct-compression method after incorporating superdisintegrants Ac-Di-Sol, Sodium Starch Glycolate (SSG), and Crospovidone in different concentrations. Nine formulations having superdisintegrants at different concentration levels were prepared to assess their efficiency and critical concentration level. Different types of evaluation parameters for tablets were used. Tablets containing Ac- Di- Sol showed superior organoleptic properties, along with excellent *in vitro* and *in vivo* dispersion time and drug release, as compared to other formulations. [38]

16. **Shirsand SB, Para MS, Swamy PV, Nagendra Kumar D, Sunil F designed fast disintegrating tablets of Prochlorperazine maleat using camphor as the subliming agent (up to 30% w/w), crospovidone and croscarmellose sodium (2-8% w/w) was used as superdisintegrant. The prepared formulations were further evaluated for hardness, friability, drug content uniformity, in vitro dispersion time, wetting time and water absorption ratio. Based on in vitro dispersion time (approximately 10-15 s), two promising formulations (one from each super-disintegrant) were tested for in vitro drug release pattern in pH 6.8 phosphate buffer. Among the two promising formulations, the formulation (SCP3) containing 8% w/w of crospovidone and 30% w/w camphor as the subliming agent emerged as the overall best formulation (t50%=6 m) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation (t50%=17.4 m).** [39]

17. **Uday S. Rangole, P. S. Kawtikwar and D. M. Sakarkar** carried out their research on formulation and *in vitro* evaluation of rapidly disintegrating tablets by direct compression technology using Hydrochlorothiazide as a model drug. Fast disintegrating tablet of hydrochlorothiazide was formulated using different concentration (2%, 3%, 4% and 5%) of superdisintegrants like Croscarmellose sodium and Crospovidone. Disintegration time and drug release were taken as the basis to optimize the rapidly disintegrating tablet. Prepared tablets were evaluated for thickness, hardness, friability, uniformity of weight, disintegration time,

wetting time and dissolution study. Crospovidone in the concentration of 4 % gives fasted disintegration in 16 sec. and shows 100% drug release within 14 min. is selected as the optimized formulation. [40]

18. **Na Zhao,and Larry L. Augsburger** investigated the influence of swelling capacity of superdisintegrants in different pH media on the dissolution of Hydrochlorothiazide From Directly Compressed Tablets. Significant reductions in the rate and extent of water uptake and swelling were observed for both sodium starch glycolate (Primojel) and croscarmellose sodium (Ac-Di-Sol) in an acidic medium (0.1 N HCl) but not for crospovidone NF (Polyplasdone XL10), a nonionic polymer. When Primojel and Ac-Di- Sol were incorporated in model formulations, a significant increase in tablet disintegration time was observed for slowly disintegrating tablets (lactose-based tablets) but not for the rapidly disintegrating tablets (dicalcium phosphate-based tablets). The dissolution rate of the model drug, hydrochlorothiazide, was found highly dependent on both tablet disintegration efficiency and the solubility of base material(s) in the testing medium. [41]
19. **R. Doijad, F. Manvi & K. D. Khalandar** formulated Granisetron mouth dissolving tablets, by incorporation of super disintegrants in the formulation and evaluated overall efficiency of them. The tablets were prepared by wet granulation method. PVP K-32 in isopropyl alcohol is used as binder. Then the granules were compressed on a Cadmach single stroke punch machine. All the four formulation showed flat, smooth tablets with 10 mm diameter. Hardness, friability, weight variation and drug content were within limits. Disintegration time of all formulations was within 60s. As the formulations F1, F2, F3 contained super disintegrants, they showed faster disintegration time, than the formulation F4. Overall the lag time for disintegration of tablet is reduced, thereby aiding pregastric absorption of granisetron. Hence first pass metabolism is minimized and oral bioavailability may be enhanced. [42]
20. **Jashanjit Singh and Rajmeet Singh** studied the formulation and optimization of orodispersible tablets of meloxicam using a 2^2 factorial design for enhanced

bioavailability. The tablets were made by non-aqueous wet granulation using crospovidone and mannitol. A 2^2 factorial design was used to investigate the amount of crospovidone and taste masking, soothening hydrophilic agent (Mannitol), as independent variables, and disintegration time as dependent response. Formulated orodispersible tablets were evaluated for weight variation, friability, disintegration time, drug content, wetting time, water absorption ratio and in vitro drug release. The results showed that the presence of a superdisintegrant and Mannitol is desirable for orodispersion. All the formulations satisfied the limits of orodispersion with a dispersion time of less than 60 sec. For example, formulation F_4 showed a disintegration time of 32.1 sec, crushing strength of 4.93 kg/cm^2, drug content of 98.5% and fast drug release rate of 99.5% within 30 min, as compared with the conventional tablet (49.5%). [(43)]

21. **Na Zhao and Larry L. Augsburger** aimed to compare the disintegration efficiency, and to develop a discriminating test model for the 3 classes of superdisintegrants represented by Ac-Di-Sol, Primojel, and Polyplasdone XL10. Using a digital video camera to examine the disintegration process of tablets containing the same wt/wt percentage concentration of the disintegrants, Ac-Di-Sol was found to disintegrate tablets rapidly into apparently primary particles; Primojel also apparently disintegrated tablets into primary particles but more slowly; Polyplasdone XL10 disintegrated tablets rapidly but into larger masses of aggregated particles. The differences in the size distribution generated in the disintegrated tablets likely contribute to the drug dissolution rate differences found for aspirin tablets with similar disintegration rates. The aspirin tablet matrix is proposed as a model formulation for disintegrant efficiency comparison and performance consistency testing for quality control purposes. [(44)]
22. **Xiaorong Hea, Michael R. Barone , Patrick J. Marsac , David C. Sperry** developed a rapidly dispersing tablet of a poorly wettable compound and carried out formulation DOE and mechanistic study of effect of formulation excipients on wetting of celecoxib. A dispersibility method was developed to study the effects of formulation excipients and processing methods on wetting of celecoxib. Results show that wet granulation facilitates better drug dispersion than does dry

granulation or direct compression. Polyplasdone XL as a disintegrant results in better celecoxib dispersibility than sodium starch glycolate. The binder Kollidon 30 leads to better dispersibility, but slower disintegration than Kollidon 12. It is found that ionic surfactant resulted in better dispersibility than a neutral surfactant, probably due to charge dispersion. Kollidon 30 gives better drug dispersion than hydroxypropylmethyl cellulose and hydroxypropyl cellulose. Dense granules were formed when the disintegrant, Polyplasdone, was added intra-granularly. As the extra-granular portion of the disintegrant increases, the dispersibility of the drug increases as well. A 3-factor face-centered experimental design was conducted to optimize the levels of surfactant (SLS), binder (Kollidon 30) and disintegrant (Polyplasdone). The level of Polyplasdone has no significant impact on the dispersibility of micronized drug; however, higher levels of Polyplasdone lead to significantly harder tablets. [45]

23. **G. Abdelbary, C. Eouani, P. Prinderre, J. Joachim, Jp. Reynier, Ph. Piccerelle** determined the in vitro disintegration profile of rapidly disintegrating tablets and found out correlation with oral disintegration. Results obtained when artificial saliva at 37 ◦C was employed as disintegration medium were used to correlate the in vitro (*t*2) and oral disintegration times. Excellent correlation was found and in addition, we were able to achieve a qualitative measure of the mouthfeel by comparing the thickness of the tablets and the penetration distance obtained from the disintegration profile. This method also permitted the discrimination between different RDT, where differences in the disintegration mechanism were reflected on the disintegration profile achieved for each tablet.[46]
24. **Jinichi Fukami , Etsuo Yonemochi , Yasuo Yoshihashi , Katsuhide Terada** prepared a rapidly disintegration tablet using a glycine as a disintegrant. Wetting time prepared from carboxymethylcellulose (NS-300) having the hardness of 4 kg was 3 s. Tablet containing NS-300 showed fastest disintegration compared to other formulations. These results suggested that NS-300 possessed excellent wetting nature and resulted in the rapid disintegration of tablet. Ethenzamide and ascorbic acid were added to the formulation, and their disintegration behavior were evaluated. Ethenzamide did not affect the disintegration property, however,

ascorbic acid prolonged disintegration time. It was suggested that the tablet formulation containing NS-300 and glycine was highly applicable to water-insoluble drug, such as ethenzamide.[47]

25. Yoshio Kuno , Masazumi Kojima , Hiroaki Nakagami , Etsuo Yonemochi , Katsuhide Terada evaluated the effect of lubricants on the characteristics of orally disintegrating (OD) tablets manufactured using the phase transition of sugar alcohol. OD tablets were produced by directly compressing a mixture containing lactose–xylitol granules, disintegrant, glidant and lubricant, and subsequent heating. The effect of the type of lubricant on the tablet characteristics was evaluated using magnesium stearate (Mg-St), sodium stearyl fumarate (SSF), and talc as lubricants. The hardness of the tablets increased to 6 kp as a result of heating, regardless of the kind of lubricant. The oral disintegration time of the tablets containing Mg-St or SSF increased with an increase in the hardness. In contrast, the oral disintegration time of the tablets containing talc was not changed despite of an increase in hardness. The water absorption rate of the tablets containing talc was much faster than that of the tablets containing other lubricants. Talc was demonstrated to be the most desirable lubricant for the preparation of OD tablets based on the principle of the phase transition of sugar alcohol. [48]
26. Sameer G. Late, Yi-Ying Yu, Ajay K. Banga I Sameer G. Late, Yi-Ying Yu, Ajay K. Banga investigated the effects of calcium silicate (disintegration-promoting agent) and various lubricants on an optimized cyclodextrin-based fast-disintegrating tablet formulation. Effects of moisture treatment were also evaluated at 75, 85 and 95% relative humidities. A two factor, three levels full factorial design was used to optimize concentrations of calcium silicate and lubricant. Magnesium stearate, being commonly used lubricant, was used to optimize lubricant concentration in optimization study and revealed that concentration of calcium silicate had no effect; however concentration of lubricant was found to be important for tablet disintegration and hardness. An optimized value of 1.5% of magnesium stearate gave disintegration time of 23.4 s and hardness of 1.42 kg. [49]

27. **Yoshio Kuno, Masazumi Kojima, Shuichi Ando, Hiroaki Nakagami** evaluated the properties of rapidly disintegrating (RD) tablets manufactured by the phase transition method.The results suggested that the heating process and xylitol content might influence the properties of RD tablets. They also evaluated the physicochemical properties of the RD tablets, including the median pore size, crystallinity, hardness, and oral disintegration time of tablets made with and without heating. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol. It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making RD tablets without any special apparatus. [(50)]

28. **Masaaki Sugimoto, Toru Maejima, Shinji Narisawa, Koji Matsubara,Hiroyuki Yoshino et al** investigated the factors affecting the characteristics of rapidly disintegrating tablets containing an amorphous ingredient prepared by crystalline transition method (CTM) under various storage conditions. Effect of storage conditions and formulating ratio of amorphous sucrose on the characteristic changes (tensile strength, porosity, and disintegration time) of the rapidly disintegrating tablets was studied. The storage conditions of different temperature and humidity affected the rate of crystalline transition and the increase in the tablet tensile strength. The higher formulating ratio of amorphous sucrose provided the longer disintegration time in the mouth. They concluded that the formulating ratio of 10–20% of the amorphous sucrose in the tablet is suitable for the rapidly disintegrating tablet in the mouth when prepared by CTM. [(50)]

29. **Simone Schiermeier, Peter Christian Schmidt** formulated water dispersible tablet and orodispersible tablet of coated Ibuprofen by direct compression method. The properties of the water dispersible tablet, such as porosity, hardness, disintegration time and increase in viscosity after dispersion, were investigated. The selected tablet formulation, containing 26% galactomannan and 5% crospovidone, disintegrates before the galactomannan starts to swell. These

tablets disperse in water within 40 s and show a crushing strength of 95 N. An optimum Orodispersable tablet formulation, containing 34% mannitol and 13% crospovidone, provides a short wetting time of 17 s and a sufficient crushing strength of 40 N. [51]

30. **Takao Mizumotoa, Yoshinori Masudaa, Takeshi Yamamotob, Estuo Yonemochi, Katsuhide Terada** investigated a novel fast-disintegrating tablet through improvement of compressibility of low compressibility saccharides, by coating and granulating the same with a high one to enable the production of a fast-disintegrating tablet. Another discovery was that the high-compressibility saccharide used as a binder solution was present in an amorphous state after the granulation process. The crystal change from amorphous to crystal state intentionally by a conditioning process after compression enabled to increase tablet hardness by strengthening adhesion between particles. The conditioning process made it possible to achieve sufficient hardness while maintaining the fast disintegration time. As a result, this fast-disintegrating tablet that can be manufactured by commonly used equipment, can be used for the dosing of a wide range drugs. [52]
31. **Iman Saad Ahmed, Mona Hassan Aboul-Einien** developed a fast-disintegrating lyophilized dry emulsion (LDE) tablet to enhance the in vitro dissolution and in vivo absorption of Griseofulvin. In this study, the rate of absorption of GF from LDE tablet was faster than that from the reference tablet and had significantly higher (p = 0.02) peak plasma concentration and shorter time to C_{max} by 4 h. Stability results, after 6 months storage of LDE tablets at 25 ◦C and 60% relative humidity, showed a slight increase in disintegration time and residual moisture content, while results from dissolution studies showed slightly slower initial drug release.[53]
32. **Hisakadzu Sunada and Yunxia Bi** developed rapidly disintegrating tablets using both direct compression and wet compression methods. Tablet properties, such as porosity, tensile strength, wetting time and disintegration time were evaluated, and the formation and disintegration mechanisms of the tablets were elucidated.

Formulation and preparation conditions were optimized using polynomial regression or artificial neural network ANN.[54]

33. **Rahul Chandrasekhar, Zahra Hassan, Farhan AlHusban, Alan M. Smith, Afzal R. Mohammed** developed and optimized FDTs using gelatin and BSG in single and combination at 1st stage. A combination (5% gelatin) FDT comprising a 50:50 ratio of 75:225 BSGs (hardness: 13.7 ± 0.9 N and disintegration time: 24.1 ± 0.6 s) was judged the most ideal, and was carried forward to Stage II: the addition of the saccharides sorbitol, mannitol and sucrose in concentrations between 10% and 80% w/w. The best properties were exhibited by mannitol-containing formulations (50%-hardness: 30.9 ± 2.8 N and disintegration time: 13.3 ± 2.1 s), which were carried forward to the next stage: the addition of viscosity-modifying polymers to improve mouth-feel and aid pre-gastric retention. Addition of carbopol 974P-NF resulted in the enhancement of viscosity with a compromise of the hardness of the tablet, whereas Pluronic F127 (6%) showed an increase in disintegration time and viscosity with retention of mechanical properties. [55]
34. **Vijay Sharma, Anil K. Philip and Kamla Pathak** developed a orodispersible tablet of roxithromycin, using modified polysaccharides as rapidly disintegrating excipients. Modified polysaccharides co grinded treated agar (C-TAG) and co grinded treated guar gum (C-TGG) were prepared by subjecting pure polysaccharides namely agar and guar gum respectively to sequential processes of wetting, drying and co grinding with mannitol (1:1). Results indicated that lower levels of modified polysaccharides namely C-TAG in F3 and C-TGG in F7 and higher levels of microcrystalline cellulose, exhibited least disintegration times without friability concerns. In vitro release of optimized formulations F3 and F7, both at salivary pH and physiological pH was found to be more than 90% within 30 min as compared to 27.82% at the same time point of conventional formulation. [56]
35. **Honey Goel, Nishant Vora, and Vikas Rana** developed and optimized fast disintegrating tablets of Ondansetron HCl (water soluble) or domperidone (water insoluble) using aminoacetic acid, carmellose and sodium alginate with enough

mechanical strength and their disintegration behaviour was evaluated. Plackett Burman Screening Design was used to screen the independent active process which were found to actively influence the dependent variables. Also, the coefficients of active variables of FDTs containing domperidone was found to be significantly different from the coefficients of active factors containing ondansetron HCl FDTs. Further, FDTs containing domperidone was prepared according to central composite design for estimating the effect of active factors in extended spherical domain. The regression analysis of quadratic fit revealed that DT, WT and WAR were 98% correlated with active factors.The optimized domperidone FDTs were further compared with superdisintegrants. The data revealed that optimized domperidone FDTs were better than domperidone FDTs containing croscarmellose or crospovidone. Hence, this novel excipients combination can be used for delivery of water insoluble drugs in place of superdisintegrants.[57]

36. **Omaima A. Sammour, Mohammed A. Hammad, Nagia A. Megrab, and Ahmed S. Zidan** prepared the MDT of rofecoxib using of its solid dispersion with polyvinyl pyrrolidone K30 (PVP K30) using solvent evaporation method. In an attempt to construct a statistical model for the prediction of disintegration time and percentage friability, a 3^2 randomized full and reduced factorial design was used to optimize the influence of the amounts of superdisintegrant and subliming agent.. Concerning the optimization study, the multiple regression analysis revealed that an optimum concentration of camphor and a higher percentage of crospovidone are required for obtaining rapidly disintegrating tablets. In conclusion, this investigation demonstrated the potential of experimental design in understanding the effect of the formulation variables on the quality of mouth dissolve tablets containing solid dispersion of a hydrophobic drug. [58]
37. **G. Abdelbary, P. Prinderre, C. Eouani, J. Joachim, J. P. Reynier and Ph. Piccerelle** described a new approach to prepare RDT with sufficient mechanical integrity, involving the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). The incorporation of Superpolystate® in the formulation of RDT was realised by means of two different granulation methods: wet granulation by using

an emulsion of this waxy binder as granulating liquid and melt granulation where the molten form of the binder was used. The potential of the intragranular addition of croscarmellose sodium as a disintegrating agent was also evaluated. The subsequent step encompassed the preparation and the evaluation of the tablets, including the effect of the extragranular introduction of croscarmellose sodium. An improvement in tablet hardness and friability was observed with both granulation methods where they were able to obtain RDT with a disintegration time of 40±2 s and a hardness of 47.9±2.5N. [59]

38. **Mutasem M. Rawas-Qalaji, F. Estelle R. Simons, and Keith J. Simons** evaluated the effect of increasing epinephrine load on the characteristics of fast-isintegrating sublingual tablets. Four tablet formulations, A, B, C, and D, containing 0%, 6%, 12%, and 24% of epinephrine bitartrate, respectively, and microcrystalline cellulose, low-substituted hydroxypropyl cellulose (9:1), were prepared by direct compression, at a range of compression forces. A linear increase in compression force resulted in an exponential increase in hardness for all formulations, a linear increase in disintegration and wetting times of A, and an exponential increase in disintegration and wetting times of B, C, and D. Tablets with drug loads from 0% to 24% epinephrine can be formulated with hardness, disintegration times, and wetting times suitable for sublingual administration. [60]
39. **Ashok R. Patel and Pradeep R.** Vavia evaluated the potential of ternary complexation as an approach for taste masking. For this purpose famotidine with property of bitter taste was selected as a model drug. Improvement in taste masking capability of cyclodextrin towards famotidine was evaluated by formulating a ternary complex including hydrophilic polymer hydroxyl propyl methyl cellulose (HPMC 5 cps) as the third component. Taste perception study was carried out on human volunteers to evaluate the taste masking ability of ternary complexation. Ternary system showed effective taste masking as compared to binary complex and at the same time showed no limiting effect on the drug release (D.E15min=90%). The effective taste masking was attributed to the enhanced complexation of famotidine in ternary system compared to binary system and the same was confirmed from the characterization studies. In

conclusion, the study confirmed that ternary complexation can be utilized as an alternative approach for effective taste masking. [61]

40. **U.S. Patent No. 4,910,023 to Botzolakis et. al.** discloses a pharmaceutical preparation comprising a poor tasting hygroscopic drug that is taste masked using from about 3% to about 30% by weight of silicon dioxide adsorbed onto the drug particle. The pharmaceutical composition is administered as swallowable capsule or tablet wherein the drug is present in amounts of from 30 to 70% of the total composition. [62]
41. **U.S. Patent No. 4,786,508 to Ghebre-Sellassie et. al.** discloses taste masking of bitter tasting drugs in oral dosage forms using a polymeric coating component that contains a cationic copolymer with residues of (meth)acrylic ester and dimethyl aminoethyl(meth) acrylate. The polymeric coating is saliva resistant yet a acid soluble for protection in the mouth and buccal area but ingestible once swallowed. [63]
42. U.S patent No. 5,681,577 to Lech Stanley et. al discloses an improved chewable cold /sinus medication comprising a decongestant pseudoephedrine , and an antihistamine, such as chlorpheniramine maleate or diphenhydramine hydrochloride. The drugs are incorporated onto an adsorbant material comprising silicon dioxide which surprisingly masks their bitter metallic taste and numbing mouth feel that would otherwise prohibit their use in a chewable tablet dosage form. [64]
43. **U.S Paten No. 6,001,392 to Wen et. al.** proposes a mixture of coated and non coated sulphonic acid cation exchange resins cross- linked with divinyl benzene on to which dextromethorphan has been loaded. [65]
44. **U.S patent no. 651,4492 to Gao et. al.** discloses formulation of oral liquid product using ion exchange resins as carriers for eliminating the bitter taste of quinolone**.** [66]
45. **U.S Patent No. 5,529,783 to Burke et. al.** discloses chewable tablet formulations comprising individual taste masked coated granules of acetaminophen, chlorpheniramine, pseudoephedrine and dextromethorphan. [67]

46. **U.S Patent No. 5466464 to Masaki et. al**. discloses a solid preparation soluble in buccal cavity, which ic composed of a sugar comprising lactose and or moannitol and 0.1-1.2% of agar and active ingredient and has a density of 400-1000 mg/ml and such a strength to withstand handling in the manufacture thereof.[68]
47. **A. Abdelbary, A.H. Elshafeey , G. Zidan** studied the Comparative effects of different cellulosic-based directly compressed orodispersable tablets on oral bioavailability of famotidine. A 32 full factorial design was used to evaluate the influence of different excipients on the properties and in vitro dissolution of famotidine ODT. Two factors were studied for their qualitative effects, namely, disintegrants and diluents. Disintegrants were studied in three levels viz. Ac-Di-Sol, sodium starch glycolate (Primojel) and low-substituted hydroxypropyl cellulose (L-HPC). Fillers were studied in three levels viz. mannitol, spray dried lactose and Avicel PH 101. The ODTs were prepared by direct compression and were evaluated for hardness, drug content, uniformity of weight, in vitro disintegration time, oral disintegration time, wetting time and in vitro dissolution. Maximum dissolution and minimum oral disintegration time (11.4 s) were observed in F7 prepared using L-HPC and mannitol. [69]
48. **Sishu et. al.** prepared fast disintegrating tablets of Diazepam using MCC as directly compressible filler and SSG as super disintegrants. The tatse masked microspheres were prepared using Eudragit E-100 by solvent evaporation technique. Successful FTD shows good taste and invivo disintegrating time 30 seconds. [70]

AIM & OBJECTIVE

- Formulation development and evaluation of orally disintegrating tablets of Dextromethorphan HBr.
- Since the taste of the drug is very bitter, suitable method for taste masking is to be developed prior to formulation development.
- The in vitro disintegration time is to be maintained within 30 seconds.
- Smooth mouth feel is to be obtained during in vivo disintegration.
- Optimization of sweeteners and flavors to obtain a palatable formulation.

PLAN OF WORK

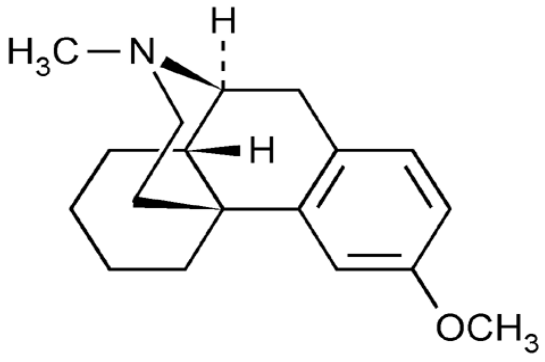
The scheme of proposed work is as fallows:

- API Characterization
  - Organoleptic Properties
- Taste-masking of API
  - By using Ion-exchange Resins
  - By using β-cyclodextrin
  - By using magnesium trisilicate.
- Characterization of API and taste masked API and pre-formulation studies
  - Physico mechanical characterization
  - Particle size distribution
  - Drug excipient compatible study
  - Moisture content
- Formulation of ODT
- Evaluation of ODT
  - Weight variation.
  - Thickness
  - Hardness
  - Friability
  - Disintegration time (DT)
  - Taste of ODT
  - Assay
  - In vitro drug release.
- Stability study

DRUG PPOFILE [72-83]

Dextromethorphan Hydrobromide

Structure:



Chemical Name: 3-methoxy-17-methyl-9,13, 14 morphinian hydrobromide monohydrate

Molecular Formula: C18H25NO ·HBr· H2O

Molecular Weight: 370.32

Physical Appearance: A practically white to slightly yellow, odorless, crystalline powder

Solubility: 1 in 65 of water; freely soluble in alcohol and in chloroform; insoluble in ether

λmax : 278nm

pH: 1% solution in water is between 5.2 and 6.5

Dose: 10 to 20 mg every 4 hours, or 30 mg every 6 to 8 hours, to a usual maximum of 120 mg in 24hours.

Bioavailability: 11%

Half life: 1.4- 3.9 hours

Taste: Bitter

Action & Use: The primary use of Dextromethorphan is as a cough suppressant, for the temporary relief of cough caused by minor throat and bronchial irritation (as commonly accompanies the common cold), as well as other causes such as inhaled irritants.

Pharmacology: Dextromethorphan is the dextrorotary-enantiomer of the opioid-receptor agonist levomethorphan . Unlike most opioids, it has not been reported to possess significant analgesic properties or dependence-liability. It is, however, a potent antitussive and has largely replaced codeine in this indication. It is perhaps the most widely available and used antitussive currently marketed.

An active metabolite of Dextromethorphan is Dextrorphan, the 3-hydroxy derivative of Dextromethorphan. The effects of Dextromethorphan are believed to be caused by both Dextromethorphan and Dextrorphan. Dextromethorphan is predominantly metabolized by the liver, by the hepatic cytochrome P450 enzyme known as CYP2D6. There is a significant proportion of the population who has a functional deficiency in this enzyme (CYP2D6 poor metabolizers). As CYP2D6 is the primary metabolic pathway in the inactivation of Dextromethorphan, the duration of action and effects of Dextromethorphan are significantly increased in such poor metabolizers. Deaths and hospitalizations have been reported in poor metabolizer recreational users.

A large number of medications (including antidepressants) are potent inhibitors of CYP2D6. There exists, therefore, the potential of drug-drug interactions between dextromethorphan and concomitant medications. There have been reports of fatal consequences arising from such interactions.

Dextromethorphan crosses the blood-brain barrier, and the following pharmacological actions have been reported:

- NMDA glutamatergic receptor antagonist
- dopamine reuptake inhibitor
- σ_1 and σ_2 receptor agonist
- $\alpha 3\beta 4$ nicotinic receptor antagonist
- serotonin reuptake inhibitor

Drug Interaction: Dextromethorphan should not be used (either recreationally or at normal dosage levels) by people who are taking a monoamine oxidase inhibitor. Combining DXM and a MAOI has been fatal. Fluoxetine (Prozac™) is a cytochrome P450-2D6 inhibitor, and will change the characteristics of a Dextromethorphan trip somewhat. The duration of the trip may be greatly extended by P450-2D6 inhibitors; some users have reported effects lasting 12 to 24 hours past the normal duration. Dextromethorphan should not be taken (recreationally or at normal dosage levels) with the prescription antihistamine Terfenadine (Seldane™). The reason for this interaction seems to be that terfenadine, which is normally metabolized by a P450 enzyme, induces heart irregularities when it builds up. Dextromethorphan may saturate the P450 enzymes that normally metabolize terfenadine.

ADR: High doses of ths drug can cause ataxia, respiratory depression and convulsions in children, while in adults high doses can alter sensory perceptions and cause ataxia, slurred speech and dysphoria. The side effects include slight drowsiness and G.I upset**.**

Use in Different Pathological Conditions: Dextromethorphan is commonly used to determine cytochrome P450-2D6 activity. Cytochrome P450-2D6, or debrisoquine 4-hydroxylase, is a liver enzyme which converts DXM into dextrorphan, and is extensively involved in the metabolism of other drugs. By looking at the metabolites of Dextromethorphan, a physician can determine P450-2D6 efficiency, and adjust drug dosage to match.

One area in which Dextromethorphan shows great promise is in the prevention of brain damage resulting from excitotoxicity (over-stimulation of nerve cells to the point of cell death) and other types of nerve cell damage. Dextromethorphan may reduce or eliminate the brain damage resulting from conditions such as fever, hypoxia (lack of oxygen), ischemia (cutoff of blood to brain cells), physical injury, infection (such as poliomyelitis, encephalitis, and mceningitis), stroke, seizure, drug toxicity, and withdrawal from long-term dependence upon certain drugs (notably alcohol, barbiturates, and benzodiazepines such as Valium™).

In the case of infection (and in particular poliomyelitis), it has been demonstrated that the damage to the CNS often occurs not from the infection, but from the body's own defenses, and notably from a chemical called quinolinic acid (a metabolite of tryptophan). Quinolinic acid is a very potent agonist (activator) at excitatory amino acid receptors, of which NMDA is one type; Dextromethorphan prevents quinolinic acid from activating NMDA receptors.

Dextromethorphan is currently being evaluated as an anticonvulsant. Preliminary studies in humans indicate that even very low levels of Dextromethorphan may help prevent seizures. This effect is not due to NMDA receptors; instead, it is probably due to sigma receptors or voltage-gated ion channels.

Another new area where Dextromethorphan has potential is in combating the withdrawal symptoms of opiate addiction. Dextromethorphan plus diazepam (Valium™) was more effective at combating the symptoms of heroin withdrawal than chlorpromazine (Thorazine™) plus diazepam. This is most likely due to Dextromethorphan's ability to block NMDA receptors. Dextromethorphan has shown some potential for treating some of the problems associated with mental retardation. It may also be of use in treating Parkinson's disease and ALS (Lou Gehrig's Disease). DXM may be useful in conjunction with opiates for alleviation of both acute and chronic pain. It may even be useful in fighting lung cancer.

EXCIPIENT PROFILE

MANNITOL [84]

1. Nonproprietary Names:

BP	JP	PhEur	USP
Mannitol	D-Mannite:	Mannitolum:	Mannitol

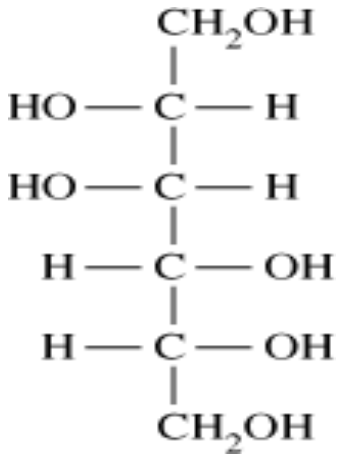
2. Synonyms: Cordycepic acid; E421; D-mannitol; manna sugar; mannite; *Pearlitol*.

3. Chemical Name and CAS Registry Number: D-Mannitol [69-65-8]

4. Empirical Formula: $C_6H_{14}O_6$

5. Molecular Weight: 182.17

6. Structural Formula:



7. Functional Category: Sweetening agent; tablet and capsule diluent; tonicity agent; vehicle (bulking agent) for lyophilized preparations.

8. Applications in Pharmaceutical Formulation or Technology: Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10-90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.

Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.

In lyophilized preparations, mannitol (20-90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. A pyrogen-free form is available specifically for this use.

9. Description: Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol.

10. Typical Properties:

Density (bulk): 0.430 g/cm^3 for powder; 0.7 g/cm^3 for granules.

Density (tapped): 0.734 g/cm^3 for powder; 0.8 g/cm^{3}for granules

Density (true): 1.514 g/cm^3

Dissociation constant: pK_a = 13.5 at 18°C

Flowability: Powder is cohesive, granules are free flowing.

Melting point: 166-168°C

Solubility: **Table-2: Solubility of Mannitol**

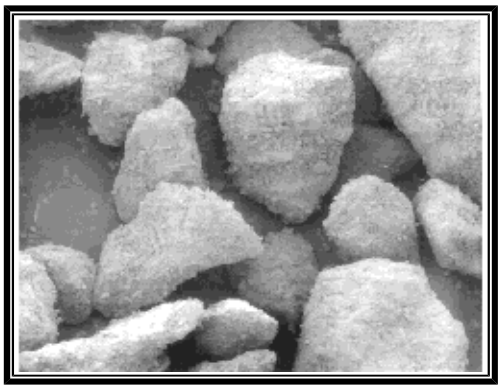
Solvent	Solubility at 20°C
Alkalis	Soluble
Ethanol (95%)	1 in 83
Ether	Practically insoluble
Glycerin	1 in 18
Water	1 in 5.5

Specific surface area: 0.37-0.39 m^2/g

Fig-5: SEM images of mannitol (Powder and granular).

SEM-Mannitol powder

Manufacturer: SPI Pharma



SEM-Mannitol granular

Manufacturer: SPI Pharma

11. Stability and Storage Conditions: Mannitol is stable in the dry state and in aqueous solutions. Mannitol does not undergo Maillard reactions. The bulk material should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities: None reported in the dry state. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

13. Handling Precautions: Mannitol may be irritant to the eyes; eye protection is recommended.

14. Regulatory Status: GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IP, IM, IV, and SC injections, infusions, buccal, oral and sublingual tablets and capsules). Included in nonparenteral and parenteral medicines licensed in the UK.

CROSSPOVIDONE[85]

Nonproprietary Names:

BP	PhEur	USP
Crospovidone	Crospovidone	Crospovidone

2. Synonyms:

Cross-linked povidone; Kollidon CL; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl- 2-pyrrolidinone homopolymer.

3. Chemical Name and CAS Registry Number: 1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

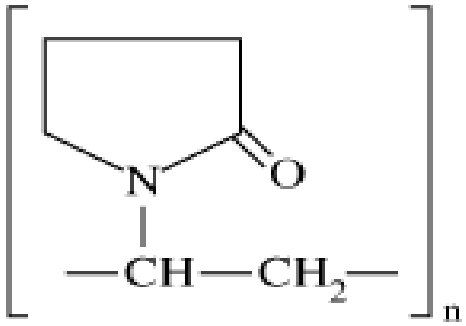
4. Empirical Formula: $(C_6H_9NO)_n$

Molecular Weight: > 1 000

Crospovidone is a water-insoluble synthetic crosslinked homopolymer of *N*-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

5. Structural Formula:

:



6. Functional Category: Tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology: Crospovidone is a water-insoluble tablet disintegrant used at 2-5% concentration in tablets prepared by direct compression or wet and dry granulation methods.[1-4] It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to form gels.

8. Description: Crospovidone is a white to creamy-white, finely divided, free- flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

10. Typical Properties

Acidity/alkalinity:	pH = 5.0-8.0 (1% w/v aqueous slurry)
Compression pressure:	20.39 kN/cm^2
Tensile strength:	0.7471 kN/cm^2
Permanent deformation pressure:	140.4 kN/cm^2
Brittle fracture index:	0.2371
Bonding index:	0.0053
Reduced modulus of elasticity:	10621
Density:	1.22 g/cm^3
Density (bulk):	0.213 g/cm^3 for Polyplasdone XL;
	0.323 g/cm^3 for Polyplasdone XL-10.
Density (tapped):	0.273 g/cm^3 for Polyplasdone XL;
	0.461 g/cm^3 for Polyplasdone XL-10.
Moisture content:	Approximately 60%.

Particle size distribution: Less than 400 µm for Polyplasdone XL; less than 74 µm for Polyplasdone XL-10. Approximately 50% greater than 50 µm and maximum of 1% greater than 250 µm in size for Kollidon CL.

Solubility: practically insoluble in water and most common organic solvents.

Specific surface area: 0.77-0.82 m^2/g

11. Stability and Storage Conditions: Crospovidone is stable. However, since it is hygroscopic it should be stored in an airtight container in a cool, dry, place.

12. Incompatibilities: Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level crospovidone may form molecular adducts with some materials.

13. Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

14. Regulatory Status: Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, topical, transdermal, and vaginal preparations).

15. Pharmacopeias: Eur and US.

CROSCARMELLOSE SODIUM[86]

1. Nonproprietary Names:

BP	JPE	USP
Croscarmellose sodium	Croscarmellose sodium	Croscarmellose sodium

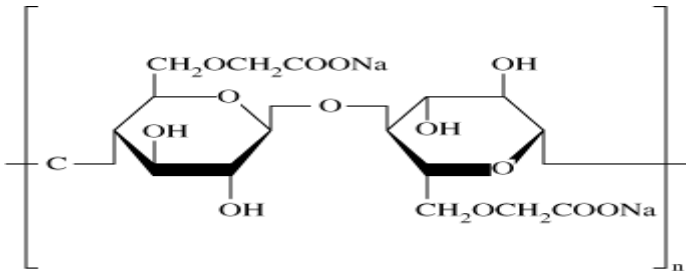
2. Synonyms: Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab.

3. Chemical Name and CAS Registry Number: Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]

4. Empirical Formula: The USP describes carboxymethylcellulose sodium as the sodium salt of polycarboxymethyl ether of cellulose.

Molecular Weight: 90 000-700 000.

5. Structural Formula:



6. Functional Category: Tablet and capsule disintegrant.

7. Applications in Pharmaceutical Formulation or Technology:

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules (10-12%w/w), tablets (0.5-5%w/w), and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression(2%) and wet-granulation(3%) processes. When used in wet granulations the croscarmellose sodium is best added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.

8. Description: Croscarmellose sodium occurs as an odorless, white-colored powder.

10. Typical Properties:

Bonding index:	0.0456
Brittle fracture index:	0.1000
Compression pressure:	20 kN/cm^2
Permanent deformation pressure:	29.9 kN/cm^2
Reduced modulus of elasticity:	960
Tensile strength:	1.3605 kN/cm^2
Density (bulk):	0.529 g/cm^3 for Ac-Di-Sol
Density (tapped):	0.819 g/cm^3 for Ac-Di-Sol
Density (true):	1.543 g/cm^3 for Ac-Di-Sol

Particle size distribution: Not more than 2% retained on a #200 (73.7 µm) mesh and not more than 10% retained on a #325 (44.5 µm) mesh, for Ac-Di-Sol. More than 90% less than 45 µm, and more than 98% less than 100 µm in size, for Pharmacel XL.

Solubility: Insoluble in water, although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water.

Specific surface area: 0.81-0.83m^2/g

11. Stability and Storage Conditions: Croscarmellose sodium is a stable though hygroscopic material. Croscarmellose sodium should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities: The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either wet-granulation or direct-compression process which contains hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

13. Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Croscarmellose sodium may be irritant to the eyes; eye protection is recommended.

14. Regulatory Status: Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

15. Pharmacopeias: Eur and US.

SODIUM STARCH GLYCOLATE[87]

1. **Nonproprietary Names**:

BP	Ph.Eur	USP
Sodium starch glycolate	Carboxymethylamylun natricum	Sodium starch glycolate

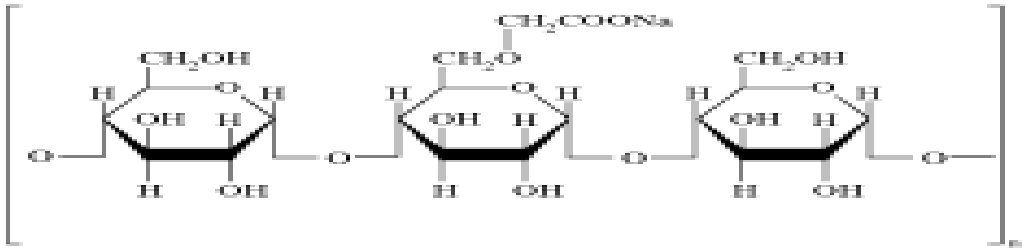
2. Synonyms: Carboxymethyl starch, sodium salt; Explotab; Primojel.

3. Chemical Name and CAS Registry Number: Sodium carboxymethyl starch [9063-38-1]

4. Empirical Formula:

5. Molecular Weight: The USP states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch. The molecular weight is typically 500 000-1 000 000.

5. Structural Formula:



6. Functional Category: Tablet and capsule disintegrant.

7. Applications in Pharmaceutical Formulation or Technology: Sodium starch glycolate acts as a disintegrant by rapid uptake of water followed by rapid and enormous swelling in capsule and tablet formulations prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2-8%, with the optimum concentration about 4% although in many cases 2% is sufficient. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients, such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.

8. Description: Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. It consists of oval or spherical granules, 30-100 µm in diameter with some less-spherical granules ranging from 10-35 µm in diameter.

10. Typical Properties

Acidity/alkalinity:	pH = 3.0-5.0% or, pH = 5.5-7.5% for a 3.3% aqueous dispersion.
Ash:	≤ 15%
Density (bulk):	0.756 g/cm$^{3(a)}$
Density (tapped):	0.945 g/cm$^{3(a)}$
Density (true):	1.443 g/cm$^{3(a)}$
Melting point:	Does not melt, but chars at approximately 200°C.

Particle size distribution: 100% of particles less than 104 µm in size. Average particle size is 42 µm for Explotab.

Solubility: Sparingly soluble in ethanol (95%); practically insoluble in water. At a concentration of 2% w/v it disperses in cold water and settles in the form of a highly hydrated layer.

Specific suface area: 0.24 m^2/g$^{(a)}$

Swelling capacity: In water, sodium starch glycolate swells up to 300 times its volume.

11. Stability and Storage Conditions: Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable and should be stored in a well-closed container to protect it from wide variations in humidity and temperature that may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 4 years if stored at moderate temperatures and humidity.

12. Incompatibilities: Sodium starch glycolate is incompatible with ascorbic acid.

13. Handling Precautions: Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. A dust mask or respirator is recommended for processes that generate a large quantity of dust.

14. Regulatory Status: Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

15. Pharmacopeias: China, Eur, and US.

MAGNESIUM TRISILICATE[88]

1. Nonproprietary Names:

BP	PhEur	USP
Magnesium Trisilicate	Magnesii trisilicas	Magnesium trisilicate.

2. Synonyms: Magnesium mesotrisilicate; silicic acid, magnesium salt (1:2), hydrate.

3. Chemical Name and CAS Registry Number: Magnesium trisilicate hydrate [39365-87-2]

4. Empirical Formula : $Mg_2Si_3O_8.xH_2O$**, Molecular Weight:** 260.86 (anhydrous)

5. Structural Formula: $2MgO.3SiO_2.xH_2O$

6. Functional Category: Anticaking agent; glidant; therapeutic agent.

7. Applications in Pharmaceutical Formulation or Technology:

Magnesium trisilicate is used in oral pharmaceutical formulations and food products as a glidant. It is also used therapeutically as an antacid.

8. Description:

The USP describes magnesium trisilicate as a compound of magnesium oxide and silicon dioxide with varying proportions of water. Magnesium trisilicate occurs as an odorless and tasteless, fine, white-colored powder which is free from grittiness.

10. Typical Properties:

Moisture content: Magnesium trisilicate is slightly hygroscopic. At relative humidities of 15-65%, the equilibrium moisture content at 25°C is 17-23%; at relative humidities of 75-95%, the equilibrium moisture content is 24-30%.

Solubility: Practically insoluble in ethanol (95%) and water.

11. Stability and Storage Conditions: Stable if stored in a well-closed container in a cool, dry, place.

12. Incompatibilities: Magnesium trisilicate may decrease the oral bioavailability of drugs such as mebeverine hydrochloride, sucralfate, and tetracycline, via chelation or binding, when they are taken together. The dissolution rate of folic acid, erythromycin stearate, paracetamol, and chloroquine phosphate may be retarded by adsorption on to magnesium trisilicate. Antimicrobial preservatives, such as the parabens, may be inactivated by the addition of magnesium trisilicate. Magnesium trisilicate is readily decomposed by mineral acids.

13. Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

14. Regulatory Status: GRAS listed. Accepted for use as a food additive in the UK. Included in the FDA Inactive Ingredients Guide (oral tablets). Included in nonparenteral medicines licensed in the UK.

15. Pharmacopeias: China, Eur, and US.

CYCLODEXTRIN[89]

1. Nonproprietary Names:

BP	PhEur	USP
Beta cyclodextrin	Betacyclodextrinun:	Beta cyclodextrin

2. Synonyms: Cyclodextrin: Cavitron; cyclic oligosaccharide; cycloamylose; cycloglucan; Encapsin; Rhodocap; Schardinger dextrin.

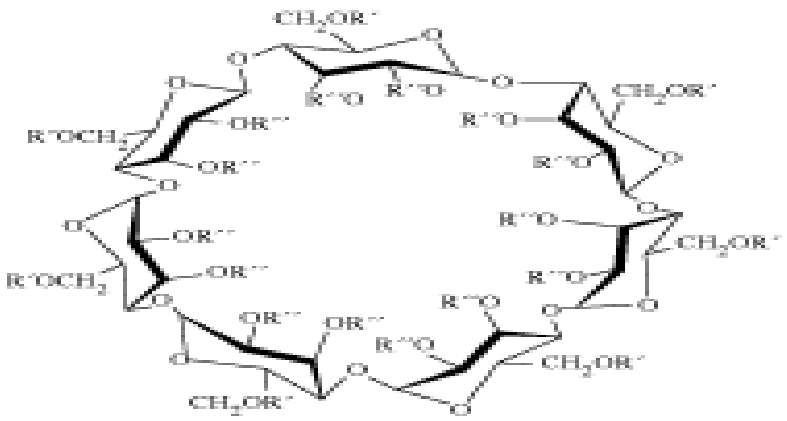
3. Chemical Name and CAS Registry Number: α -Cyclodextrin: [10016-20-3]

β - Cyclodextrin: [7585-39-9]

γ -Cyclodextrin: [17465-86-0]

4.	**Empirical Formula**	**Molecular Weight**
α-Cyclodextrin	$C_{36}H_{60}O_{30}$	972
β-Cyclodextrin:	$C_{42}H_{70}O_{35}$	1135
γ -Cyclodextrin:	$C_{48}H_{80}O_{40}$	1297

5. Structural Formula:



R', R'' = -H for 'natural' α-, β- and γ-cyclodextrins.

R', R" = $-CH_3$ for methyl cyclodextrins.

R', R" = $-CHOHCH_3$ for hydroxyethyl cyclodextrins.

R', R" = $-CH_2CHOHCH_3$ for 2-hydroxypropyl cyclodextrins.

6. Functional Category: Stabilizing agent; solubilizing agent, taste masking agent.

7. Applications in Pharmaceutical Formulation or Technology: Cyclodextrins may be used to form inclusion complexes with a variety of drug molecules resulting primarily in

improvements to dissolution and bioavailability due to enhanced solubility and improved chemical and physical stability.Cyclodextrin inclusion complexes have also been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material.However, β -cyclodextrin should not be used in parenteral formulations since it is nephrotoxic, β -Cyclodextrin is considered to be nontoxic when administered orally and has thus become primarily used in tablet and capsule formulations. β Cyclodextrin derivatives tend to be nontoxic when used either orally or parenterally and the derivatives 2-hydroxypropyl- β -cyclodextrin and 3-hydroxypropyl- β -cyclodextrin are becoming of increasing importance in pharmaceutical formulations.In oral tablet formulations β -cyclodextrin may be used in both wet granulation and direct compression processes. β -cyclodextrin tends to possess poor flow properties and requires a lubricant, such as 0.1% w/w magnesium stearate, when it is directly compressed.In parenteral formulations, cyclodextrins have been used to produce stable and soluble preparations of drugs that would otherwise have been formulated using a nonaqueous solvent. Cyclodextrins have also been used in the formulation of solutions, suppositories, and cosmetics.

8. Description: Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

9. Typical properties: Table-3: Typical properties of three types of cyclodextrin

Typical Properties	α cyclodextrin	β cyclodextrin	γ cyclodextrin
Bulk	0.526 g/cm^3	0.523 g/cm^3	0.568 g/cm^3
Tapped	0.685 g/cm^3	0.754 g/cm^3	0.684 g/cm^3
True	1.521 g/cm^3	1.378 g/cm^3	1.471 g/cm^3
Melting point:	250-260°C	255-265°C	240-245°C
Moisture content: 10.2% w/w	13-15% w/w	8-18% w/w	

Specific rotation $[\alpha]_D^{25}$	+150.5°	+162.0°	+177.4°
Surface tension:	71 dynes/cm	71 dynes/cm	71 dynes/cm

Solubility: α-cyclodextrin: soluble 1 in 7 parts of water at 20°C, 1 in 3 at 50°C.

β -cyclodextrin: soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20°C, 1 in 20 at 50°C; practically insoluble in acetone, ethanol (95%), and methylene chloride.

γ -cyclodextrin: soluble 1 in 4.4 parts of water at 20°C, 1 in 2 at 45°C.

11. Stability and Storage Conditions: β -Cyclodextrin, and other cyclodextrins, are stable in the solid state if protected from high humidity.Cyclodextrins should be stored in a tightly sealed container, in a cool, dry, place.

12. Incompatibilities: The activity of some antimicrobial preservatives in aqueous solution can be reduced in the presence of hydroxypropyl-β- cyclodextrin.

13. Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Cyclodextrins are fine organic powders and should be handled in a well-ventilated environment. Efforts should be made to limit the generation of dust which can be explosive.

14. Regulatory Status: Included in oral and rectal pharmaceutical formulations licensed in Europe, Japan and the US.

SODIUM STEARYL FUMARATE[90]

1. Nonproprietary Names: USP: Sodium stearyl fumarate

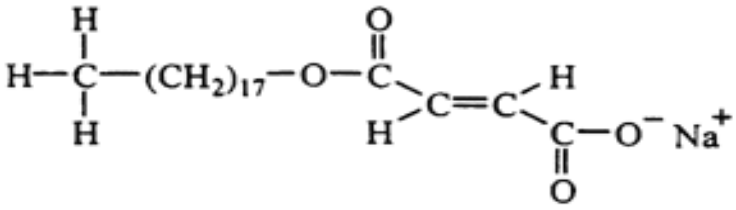
2. Synonyms: Fumaric acid, octadecyl ester, sodium salt; Pruv; sodium monostearyl fumarate.

3. Chemical Name and CAS Registry Number: 2-Butenedioic, monooctadecyl ester, sodium salt [4070-80-8].

4. Empirical Formula: **Molecular Weight:**

$C_{22}H_{39}NaO_4$ 390.5

5. Structural Formula:



6. Functional Category: Tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology: Sodium stearyl fumarate is used as a lubricant in capsule and tablet formulations at 0.5-2.0% w/w concentration. It is also used in certain food applications.

8. Description: Sodium stearyl fumarate is a fine, white powder with agglomerates of flat, circular-shaped particles.

10. Typical Properties:

Acidity/alkalinity: pH = 8.3 for a 5% w/v aqueous solution at 90°C.

Density: 1.107 g/cm^3.

Density (bulk): 0.2-0.35 g/cm^3

Density (tapped): 0.3-0.5 g/cm^3

Melting point: 224-245°C (with decomposition)

Specific surface area: 1.2-2.0 m^2/g.

Solubility: **Table-4: Solubility of SSF**

Solvent	Solubility at 20°C Unless otherwise stated
Acetone	Practically insoluble
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Methanol	Slightly soluble
Water	1 in 20 000 at 25°C,1 in 10 at 80°C,1 in 5 at at 90°C

11. Stability and Storage Conditions: At ambient temperature, sodium stearyl fumarate is stable for up to 3 years when stored in amber glass bottles, with polyethylene screw caps. The bulk material should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities: Sodium stearyl fumarate is reported to be incompatible with chlorhexidine acetate.

13. Handling Precautions: Sodium stearyl fumarate should be handled in a well-ventilated environment; eye protection is recommended.

14. Regulatory Status: GRAS listed. Permitted by the FDA for direct addition to food for human consumption as a conditioning or stabilizing agent in various bakery products, flour thickened foods, dehydrated potatoes, and processed cereals up to 0.2-1.0% by weight of the food. Included in nonparenteral medicines licensed in the UK. Included in the FDA Inactive Ingredients Guide.

15. Pharmacopeias: US

MINT FLAVOR[91]

1. Nonproprietary Names:

BP	JP	PhEur	USP
Racementhol	*dl*-Menthol	Mentholum racemicum	Menthol

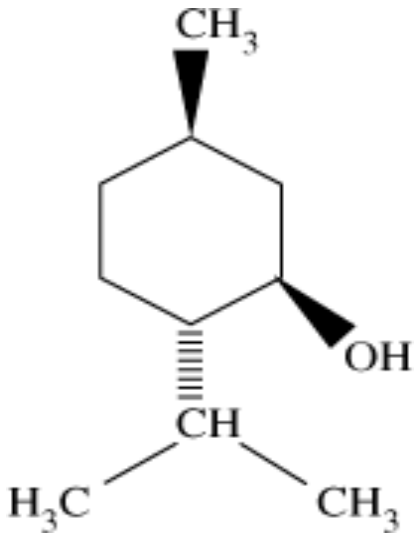
2. Synonyms: Hexahydrothymol; 2-isopropyl-5-methylcyclohexanol; 4-isopropyl-1-methylcyclohexan-3-ol; 3-*p*-menthanol; *p*-menthan- 3-ol; *dl*-menthol; peppermint camphor; racemic menthol.

3. Chemical Name and CAS Registry Number: (1*RS*, 2RS,5RS)- (±)-5-Methyl-2-(1-methylethyl) cyclohexanol [15356-70-4].

4. Empirical Formula: Molecular Weight:

$C_{10}H_{20}O$ 156.27

5. Structural Formula:



6. Functional Category: Flavoring agent; therapeutic agent.

7. Applications in Pharmaceutical Formulation or Technology: Menthol is widely used in pharmaceuticals as a flavoring agent or odor enhancer.

Table-5: % concentration of mint flavor used in different dosage forms.

Use	Concentration (%)
Inhalation	0.02-0.05
Oral suspension	0.003
Oral syrup	0.005-0.015
Tablets	0.2-0.4
Topical formulations	0.05-10.0
Toothpaste	0.4
Mouthwash	0.1-2.0

8. Description: It is a free-flowing or agglomerated crystalline powder or colorless, prismatic or acicular shiny crystals, with a strong characteristic odor and taste. The crystalline form may change with time due to sublimation within a closed vessel.

10. Typical Properties:

Boiling point: 212°C

Flash point: 93°C

Melting point: 34-36°C

Refractive index: $n_D^{20} = 1.4615$

Solubility: Very soluble in ethanol (95%), chloroform, and ether; very slightly soluble in glycerin; practically insoluble in water.

Specific rotation: $[\alpha]_D^{20}$: -2 to +2° (10% w/v alcoholic solution)

11. Stability and Storage Conditions: Menthol should be stored in a well-closed container at a temperature not exceeding 25°C, since it sublimes readily.

12. Incompatibilities: Incompatible with b-naphthol, butylchloral hydrate, camphor, chloral hydrate, chromium trioxide, phenol, potassium permanganate, pyrogallol, resorcinol, and thymol.

13. Handling Precautions: May be harmful by inhalation or ingestion in large quantities; may be irritant to the skin, eyes, and mucous membranes. Eye protection and gloves are recommended.

14. Regulatory Status: Included in the FDA Inactive Ingredients Guide. Included in nonparenteral medicines licensed in the UK. Accepted for use in foods and confectionery as a flavoring agent of natural origin.

SUCRALOSE[92]

1. Nonproprietary Names: USP NF: Sucralose

2. Synonyms: Splenda; TGS; 1',4', 6'- Trichloro galactosucrose; 4,1',6'-trichloro-4,1'6'-trideoxy- galacto-sucrose.

3. Chemical Name and CAS Registry Number: 1,6- dichloro- 1,6 deoxy –β –D-fructofuranosyl-4-chloro-4-deoxy –α- D-galactopyraside [56038-13-2].

4. Empirical Formula: Molecular Weight:

$C_{12}H_{19}Cl_3O_8$ 397.64

5. Structural Formula:

6. Functional Category: Sweetening agent.

7. Applications in Pharmaceutical Formulation or Technology: Sucralose is used as a sweetening agent in beverages, foods and pharmaceutical applications. It has sweetening power approximately 300-1000 times that of sucrose and has no after taste. It has no nutritional value, is noncariogenic, and produces no glycemic response.

8. Description: It is a white to off white colored free flowing, crystalli8ne powder.

10. Typical Properties

Melting point:	130°C for anhydrous crystalline form, 36.5°C for pentahydrate
Refractive index:	1.33-1.37
Solubility:	Freely soluble in ethanol (95%), methanol, water; slightly soluble in ethyl acetate.
Specific rotation:	$[\alpha]^{20}_{D}$: +84˚ to +87.5 (1%w/v aqueous solution); + 68.2(1.1% w/v in ethanol).
Acidity/ Alkalinity:	pH 5-6 (10%w/v aq solution at 20˚ C)
Bulk density:	0.35gm/ cc.
Tapped density:	0.62gm/cc
True density:	1.63gm/cc
Particle size distribution:	90%(<12 μ)
Partition coefficient: $\log_{10}$ P:	0.51(octanol :water)
Viscosity:	0.6-3.8 mPas.

11. Stability and Storage Conditions: Menthol should be stored in a well-closed container at a temperature not exceeding 25°C, since it sublimes readily.

12. Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handling.

13. Regulatory Status: The FDA, in April 1998, approved sucralose for use as a tablet top sweetener and as an additive in a variety of food products. In UK, Sucralose was authorized for use in food products on a 2 year temporary basis in march 2002.

AMMONIUM GLYCYRRHIZINATE[93]

1. Definition: Mixture of ammonium 18a- and 18b-glycyrrhizate (ammonium salt of (20b)-3b-[[2-*O*-(b-D-glucopyranosyluronic acid)-a-D-glucopyranosyluronic acid] oxy]-11-oxoolean-12-en-29-oic acid), the 18b-isomer being the main component.

2. Synonyms: Glycyrrhizic acid monoammonium salt.

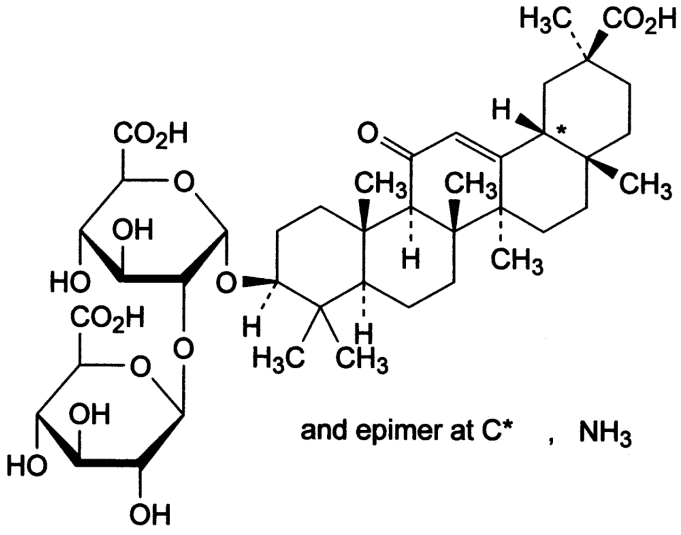
3. Molecular formula: $C_{42}H_{65}NO_{16}$

4. Molecular weight: 840

5. SAS Reg No: 53956-04-0

6. Pharmacopoeia: Ph Eur

7. Structure:



8. Content: 98.0 per cent to 102.0 per cent (anhydrous substance).

9. Application: Glycyrrhizinic acid is potentially 50 times sweeter than sucrose. Glycyrrhiza is the active principle for sweetening, flavoring and pharmaceutical applications. It is effective in treatment of peptic ulcer. It is frequently used in medicines to mask the unpleasant flavors.

10. Typical Properties:

Appearance: White or yellowish-white, hygroscopic powder.

Solubility: Slightly soluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in acetone. It dissolves in dilute solutions of acids and of alkali hydroxides.

Melting Point: 209^0 C

Contents: 98%

LOD: 6%

Specific optical rotation: + 49.0 to + 54.0 (anhydrous substance).

Water: Maximum 6.0 per cent, determined on 0.250 g.

Related substances: 18 α-Glycyrrhizic acid.

11. Stability: Stable in normal condition. Moisture sensitive.

12. Storage: In an airtight container.

EXPERIMENTAL WORK

Table-6: List of equipments & instruments used

Sl. No.	Equipment	Company/ /model
1	Mechanical stirrer.	RZR 2041, Heidolph.
2	Vacuum pump	Serve well
3	Tablet compression machine	Minipress –II SF, Rimek.
4	Tablet tester	Dr. Schleuniger 8m, Pharmatron.
5	Disintegration tester (USP)	ED-2, Sapo, Electrolab.
6	Friabilator (USP)	EF-1W, Electrolab.
7	Precision balance	AB 204-S, Mettler Toledo.
8	Electromagnetic sieve shaker	EM 8-8
9	Tap density tester (USP)	ETD 1020, Electrolab.
10	Dissolution tester (USP)	TDT- 08l, Electrolab.
11	U. V Spectrophotometer	Pharmaspec-1700, Shimadzu.
12	DSC	DSC-60, Metller Toledo.
13	Laboratory centrifuge	R-8C, Remi.
14	Infra red moisture analyzer	MA 100, Sartorious.
15	pH meter	Cyberscan 1000.

16	Sonicator	Mu 12000, markultra sonics.
17	Induction cap sealer	Sigma JR, Electronic devices.
18	Microbalance	MX 5, Mettler Toledo.
19	Stability chamber	Thermolab.

Table-7: List of materials used and their suppliers.

Sl. No.	Name of the materials	Name of the supplier
1	Dextromethorphan HBr	Divi's laboratory.
2	Amberlite IRP 64	Rohm & Haas.
3	Cyclodextrin	Roquette.
4	Magnesium trisilicate	SPI Pharma Inc.
5	Mannitol(Mannozem EZ)	SPI Pharma Inc.
6	Crosspovidone(Polyplasdone XL)	ISP Technologies Inc.
7	Sodium starch glycolate	DMV International.
8	Croscarmelose sodium	DMV International.
9	Pharmaburst™	SPI Pharma Inc.
10	Sucralose	Alkem laboratories
11	Monoammoniumglycirryzinate	Chemiloids.
12	Spermint flavor	Wild

13	SSF(Lubripharm)	SPI Pharma Inc.

PREFORMULATION STUDIES

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.

Followings are the test performed for the preformulation study.

1. Organoleptic characteristics
2. Physico mechanical characterization
3. Particle size distribution
4. Moisture content
5. Compatibility study

1. Organoleptic Characteristic:

The color, odor, and taste of the drug were characterized and recorded using descriptive terminology.

2. Physico-mechanical characterization:

a) Density measurement:

Bulk Density: It refers to packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in mg/ml.

Procedure: Weighed quantity of API was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by drug was measured. Bulk density was measured by using formula.

Tapped density: It is the ratio of mass of powder to the tapped volume. Tapped volume is the volume occupied by the same mass of powder after a standard tapping of a measure.

Procedure*:* Weighed quantity of drug was taken into a graduated cylinder. Volume occupied by the drug was noted down. Then the cylinder was subjected to 500, 750 &1250 taps in tap density tester (Electro Lab USP II). According to USP, the blend was subjected for 500 taps. The % volume variation was calculated and subjected for additional 750 taps. The % variation is calculated.

b) Flow properties:

Carr's Index (Compressibility): The Carr's index and Hausner's ratio are measures of the propensity of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It is indicated as Carr's compressibility index and is calculated as follows.

Carr's index = [Tapped density - Bulk density/Tapped density] X 100

Hausner's ratio: It is measurement of frictional resistance of the drug .It is the determined by the ratio of tapped density and bulk density

Hausner's ratio = Tapped density / Bulk density

Table-8: Interpretation of Powder Flow

% Compressibility Index	Flow Character	Hausner Ratio
≤ 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Angle of Repose (AOR):

It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane, which is given by the equation:

$$\theta = \tan^{-1} h/r$$

Where θ = Angle of repose

h = Height of the pile

r = Radius of the base of the conical pile

Procedure*:* Weighed quantity of the drug was passed through a funnel fixed at a height of 2 cm from the base. The powder is passed till it forms a heap and touches the tip of the funnel. The radius was measured and AOR was calculated by using above formula.

3. Particle size distributions:

For many active substances, particle size has an impact on powder flow, content uniformity and drug dissolution. In order to assure consistent product quality, the particle size of the API has been characterised. Electromagnetic sieve shaker was used to determine the particle size of API and drug resin complex.

4. Moisture content:

The substance to be tested was mixed and accurately weighed, and, unless otherwise directed in the individual monograph, the moisture content was determined on 1 to 2 g. If the test specimen is in the form of large crystals, the particle size should be reduced to about 2 mm by quickly crushing. A clean aluminium pan was taken and placed upon the pan holder and tared. The accurate amount of the material to be analyzed was taken and spread on the plate in such a way that a thin layer of uniform thickness is formed. The analysis specifications were set and test was performed for specified time.

5. Drug-Excipients Compatibility Study:

Protocol for drug-excipients compatibility:

(a) Drug: Excipients Ratio

Drug and excipients were taken in the ratios as mentioned in following Table No. 9. For formulations containing complex of drug and complexing agents or adsorbate of drug and adsorbents, drug excipients compatibility study was carried out taking drug complex/adsorbate and excipients ratio.

(b) Pack details

Clear transparent glass vials with rubber stopper and aluminum seal and polybags.

(c) Storage condition

1. Initial sample at room temperature
2. Polybags at 40°C/75 % RH for 4 weeks
3. Glass vials at 60ºC for 15 days.

(d) Test to be performed: Physical observation.

Procedure: Drug rein complex and excipients were thoroughly mixed in predetermined ratio given in Table No. 9 and passed through the sieve no. 60. The blends were filled in self sealable polybags and colorless transparent glass vials closed with gray rubber stoppers sealed with aluminum seal and charged in to condition at 40°C/75 % RH for 4 weeks and 60°C for 15 days respectively. Similarly API was also subjected to same conditions and time periods as that of sample.

Table-9: Drug-Excipients Compatibility Study & initial physical observations

Name of Sample	**% weight Ratio**	Observation
Dextromethorphan HBr	100:0	White crystalline powder.
Drug resin complex	100:0	Slight off white powder, free flowing. No aggregates
DRC+ Mannitol	50:50	White powder, free flowing. No aggregates
DRC+ Pharmaburst™	30:70	White powder, free flowing. No aggregates
DRC+ Crospovidone XL	95:5	Slight off White powder, free flowing. No aggregates
DRC+ Croscarmellose Sodium	95:5	Slight off White powder, free flowing. No aggregates
DRC+ Sodium starch glycolate	95:5	White powder, free flowing. No aggregates
DRC+ Sucralose	99:1	White powder, free flowing. No aggregates
DRC+ MAG	99:1	White powder, free flowing. No aggregates
DRC+ Spearmint	95:5	White powder, free flowing. No aggregates
DRC+ Citric acid	95:5	White powder, free flowing. No aggregates
DRC+ Magnesium Trisilicate	15:85	White powder, free flowing. No aggregates
DRC+ SSF	97:3	White powder, free flowing. No aggregates

Physical observation: Physical observation of each sample was carried out every week, for any color change or lumps or color formation and flow.

TASTE MASKING OF API

Taste-Masking Using Ion-Exchange Resins:

Procedure for taste-masking:

Method I:

Accurate quantity of resin was weighed and shifted it through sieve no. 60. Little amount of purified water (HPLC grade) was added and a paste was made using mortar and pestle by kneading for specified time. Required amount of drug in small quantities was added gradually and continuing kneading for specified time and the paste was dried at 60º C for 2 hours.

Method II:

Required quantity of purified water was taken and ion-exchange resin was gradually added to it, under the continuous stirring condition. Allow it to soak for 30 minutes under continuous stirring (500 RPM). Dextromethorphan HBr was added in bulk and keept it under stirring condition for 3 hours. pH was adjusted to desired level if required. After stirring for specified time the drug resin complex was collected by vacuum filtration using Whatman filter paper 41 and the resinate was dried at 60ºC. This drug-resin mixture was used for further study of assay and taste evaluation. The taste evaluation was done by volunteers and recorded using descriptive terminology. The results of drug ion-exchange resin complexation have been shown in Table No. 23.

Taste masking using β-Cyclodextrin:

Procedure for taste masking:

- **Method I (Physical mixture):** Accurately weighed drug and cyclodextrin was taken in a poly bag and mixed for 30 minutes.
- **Method II (Kneading):** Accurate quantity of cyclodextrin was weighed and shifted it through sieve no 60. Little amount of purified water (HPLC grade) was added and a paste was made using mortar and pestle by kneading for specified time. Required amount of drug in small quantities was gradually added and

continuing kneading for specified time and the paste was dried at 45º C for 2 hours. The results of drug-cyclodextrin complexation have been shown in Table No. 24

Taste masking using Magnesium trisilicate:

- **Method I (Kneading):** Accurate quantity of magnesium trisilicate was weighed and shifted through sieve no 40. Little amount of purified water (HPLC grade) was added and a paste was made using mortar and pestle by kneading for specified time. Required amount of drug in small quantity was added and continuing kneading for some time and dried the paste at 60º C for 2 hours. The results of drug-magnesium trisilicate complexation have been shown in Table No. 25.
- **Method II ((Kneading):** Required amount of magnesium trisilicate was taken in a mortar and dissolved in small amount of water at 70-80^{o} C. The drug solution was added to the magnesium trisilicate and kneaded for specified time and dried at 60^{o}C for 2 hours.

Detection of copmplexation by Differential Scanning Calorimetry:

The DSC thermograms of successfully taste masked drug complex were recorded on a Metller Toledo DSC-60. Samples of drug complex of 2 mg were heated in hermetically sealed aluminum pans over a temperature range of 50^{o} C to 200^{o} C at a constant rate of 5^{o} C/ minute under nitrogen purge. The results of DSC studies have been shown in Figure No. 12-16.

FORMULATION OF ORALLY DISINTEGRATING TABLET

Selection of Excipients:

The excipients were selected from the drug excipient compatibility study and used in the final formula within the limit of inactive ingredient guide available by FDA**.**

Selection of flavoring agent:

In the preparation of orally disintegrating tablets, taste and flavor is considered as the most essential criteria. To attain good palatability, flavoring agents are added to the formulation. Two flavoring agent; spearmint flavor and cherry flavor were selected and incorporated in the placebo blend. Placebo tablets were compressed by direct compression using 9.5mm FFBE and evaluated for taste and mouth feel. To observe taste and mouth feel 10 volunteers were selected and their comments were recorded in Table No. 18 according to the descriptive terminology tabulated in Table No. 10.

Optimization of Flavoring Agent for Pleasant Mouth Feel: Optimization of concentration of selected flavoring agent was done by incorporating 0.5%, 1%, 1.5% w/w concentration of selected flavoring agent and compressing placebo tablets using same tooling. To observe the taste and mouth feel 10 volunteers were selected and results have been tabulated in Table No 19.

Table - 10: Flavor selection and optimization scale

Remarks	Ratings
Bad	B
Average	A
Good	G
Excellent	E

PROCEDURE FOR PREPARATION OF TABLETS:

Step 1: Dispensing

Required quantity of Dextromethorphan HBr and other excipients were accurately weighed, according to the trial formulation.

Step 2: Shifting

Diluent and disintegrants were passed through # 40 mesh, drug resin complex, flavor, and lubricant were passed through # 60 mesh, either alone or in combination with other excipients.

Step 3: Mixing/Blending:

The blend of drug resin complex and other excipients were blended well using a double cone blender at 100 rpm for 10 min.

Step 4: Direct compression:

Orally disintegrating tablets were prepared by direct compression of the prepared blend using 9.5 mm FFBE punches at a Rimek Minipress 8 station single rotary tablet compression machine.

EVALUATION OF COMPRESSED TABLETS:

All the tablets were evaluated for different parameters as appearance, uniformity of weight, thickness, hardness, friability, in-vitro disintegration time, assay and in-vitro dissolution study.

Appearance:

The general appearance and elegance of tablet was identified visually, which include tablet color, shape, surface texture.

Uniformity of weight: Twenty tablets were weighed individually and collectively and then average weight was determined. The individual tablet weight was compared with average tablet weight.

Thickness, diameter and hardness:

Tablets were selected at random from individual formulations and thickness, diameter and hardness were measured by using Schleuninger tablet tester instrument which permits accurate measurement of these parameters.

Friability:

Friability is related to tablet's ability to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of Roche type friability test apparatus. Compressed tablets that loose less than 1.0% in weight are generally considered acceptable.

Method*:* Tablets were weighed accurately (initial wt.), transfer into friabilator and subjected to 100 revolutions in 4 minutes. The tablets are collected, dedusted and reweighed (final wt). These two weights were applied to following formula and friability was calculated.

$$\% \text{ Friability} = \frac{\text{(Initial Weight – final weight)}}{\text{(Initial weight)}} \times 100$$

Disintegration test:

The disintegration time was measured by using USP disintegration test apparatus. 6 tablets were placed in tubes and the basket is kept positioned in a 1-litre beaker containing 800 ml of water maintained at 37±2°C. The tablet remain 2.5 cm from the bottom of water, a standard motor driven device move the basket containing tablet up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. The time taken for complete disappearance of each tablet was recorded.

Dissolution study: The release rate of Dextromethorphan Hydrobromide from orally disintegrating tablets was determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of 0.1N HCl at 37±0.5°C and 50 rpm.

Taste and mouth feel evaluation:

Taste and mouth feel evaluation was performed by in vivo disintegration on 10 healthy human volunteers. One tablet was held in the mouth after rinsing and the time required for complete disintegration of the tablet was recorded. The disintegrsted material was held in the mouth for another 60 seconds and spat out. The mouth was rinsed with water without swallowing the disintegrated material and finally the roughness levels were recorded on a numerical scale ranging from 0 to 5, where 0,1,2,3,4,5 indicate bitter, bitter after, no bitter, pleasant, pleasant taste and good mouth feel, pleasant taste and excellent mouth feel. An adequate time interval was maintained between each evaluation to avoid confusion.

Table-11: Taste and Mouth Feel Evaluation Scale

TASTE	RATING
Bitter	0
Less Bitter	1
No Bitter Taste	2
Pleasant taste	3
Pleasant taste & Good Mouth Feel	4
Pleasant taste & excellent Mouth Feel	5

Selection of Optimized Formulation:

The optimized formulation of Dextromethorphan ODT was selected from the formulation trials and on the basis of Taste, assay, disintegration time, physical appearance of tablets, and in vitro dissolution study

STABILITY STUDY:

Stability testing of drug products begins as a part of formulation development and ends with the demise of the compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use.

The ICH Guidelines have established that long term stability testing should be done at 25ºC/60% RH; stress testing should be done at 40ºC/75%RH for 6 months. If significant change occurs at these stress condition, then the formulation should be tested at an intermediate condition i.e. 30ºC/75%RH. Table shows different temperatures and period of stability testing.

Table-12: ICH guide lines for storage conditions and time period stability study

Study	Storage condition	Time period
Long term	25°c±2°C/60%± RH5%RH or 30°c±2°C/65%RH±5% RH	12 month
Intermediate	30°c±2°c/65% ±RH5% RH	6 month
Accelerated	40°c±2°c/75%± RH5% RH	6 month

In the present work stability study was carried out for the optimized formulation for following packaging, condition and time period.

- 40°C±2°C/75% RH±5% RH in HDPE bottles and PVC PVDC 60 GSM blisters.

.

RESULTS AND DISCUSSIONS

Pre-formulation studies:

Table-13: Organoleptic Characteristics of Dextromethorphan HBr

Properties	Results
Color	White to off white
Taste	Very bitter
Odor	Odorless

Table-14: Particle size distribution of Dextromethorphan HBr

Particle size(µ)	%w/w
600	2.4
420	1.2
250	26
177	3.6
149	9.2
<149	58.8

Table-15: Bulk Properties of Dextromethorphan HBr

S. No	Parameters	Results
1	Bulk Density	0.4
2	TappDensity	0.57
3	Carr's index	29.82

4	Hausner's ratio	1.42
5	Angle of repose	30.3

The physico mechanical properties of the drug such as particle size distribution, angle of repose, bulk density and tapped density, compressibility index (CI), and Hausner's Ratio were determined. The results are presented in the Table no.14 and 15. Since 58.8% w/w of API contains particles of size <149µ, the ODTs prepared by direct compression will show good content uniformity. The CI and angle of repose of Dextromethorphan was found to be 29.82 and 30.3 indicating that the drug has poor flow properties and poor compressibility. Since the drug is to be used as the resinate in final formulation the physico mechanical propreties of resinate is also to be determined.

Table-16: Taste Masking Trials by Ion Exchange resin

B.NO	**TM1**	**TM 2**	**TM 3**	**TM 4**	**TM 5**	**TM 6**	**TM 7**	**TM 8**
Drug:A.IPR64	1:1	1:2	1:3	1:3	1:3	1:2	1:3	1:3
Method	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry	Wet mass
Soaking time(min)	30	30	30	60	30	30	30	---
pH Adjustment	NA	NA	6.5	6.5	8.0	8.0	8.0	---
Stirring time(hr)	1	1	2	2	2	2	4	---
Kneading time(min)	---	---	---	---	---	---	---	30
Drying time at 60°C(hrs)	2	2	2	2	2	2	2	2
Taste	Bitter	Bitter	Less Bitter	Less Bitter	Taste less	Less bitter	Taste less	Bitter
%Drug in Resinate	10.24	14.84	19.82	19.84	22.8	17.7	22.78	NA

Result & Discussion: As presented in above table the resinate of B.No. TM1, TM2 and TM8 were found as bitter. Comparatively less bitter resinates were obtained from B.No TM3, TM4 and TM6, but complete taste masking was not achieved. Resinate of B.No

TM5and TM7 was found to be completely taste masked. The results completely demonstrated that efficient taste masking as well as high drug loading was achieved with subsequent increase in the amount of resin in drug: resin ratio and pH of the complexing medium. At higher amount of resin and higher pH, maximum dissociation of –COOH group of the resin takes place and subsequently the number of sites for drug binding increases. Soaking process was fixed to 30 minutes and the complexation process was fixed to 2 hour as the drug loading showed no significant change. So B.No. TM5 was selected as the optimum process for taste masking by ion-exchange resin.

Table-17: Taste Masking Trials By β Cyclodextrin

B.No	**TM 9**	**TM 10**	**TM 11**	**TM 12**
Drug: CD	1:5	1:5	1:5	1:10
Method	Physical mixture	Kneading	Kneading	Kneading
Kneading time	30 min	30 min	60 min	60 min
Water	---	q. s	q. s	q. s
BitterBitterLess bitter**Drying time at 45°C(hour)**	**2**	**2**	**2**	**2**
Bitter Taste				

Result & Discussion: Only the B. No TM12 shows some extent of taste masking but it was not taste less. Bitter after taste was felt. Other trials do not show any taste masking.

Table-18: Taste Masking Trials by Magnesium trisilicate

B.No	**TM13**	**TM14**	**TM 15**	**TM16**
Drug: MTS	1:5	1:5	1:5	1:7.7
Method	Kneading	Kneading	Kneading	Kneading
Kneading time	30 min	30 min	60 min	60 min
Medium	Cold water	Hot water	Hot water	Hot water
Drying time at 60°C (Hour)	2	2	2	2
Taste	Bitter	Bitter	Bitter	Less bitter

Result & Discussion: Only the B. No TM 16 shows some extent of taste masking but it was not completely taste less. Less bitter taste was felt. Other trials do not show any taste masking.

Detection of complexation:

DSC study of Drug resin complexation:

DSC thermogram of Dextromethorphan HBr API, Amberlite IRP64, drug resin complex prepared at pH6, pH8, and pH10 has been shown in Figure No. 8-12 respectively. DSC thermogram showed a sharp endothermic peak at 117.55°C. DSC thermogram of Amberlite IRP64 showed a broad endothermic peak between 25.56°C- 99.55°C. DSC thermogram of drug resin complex prepared at pH6 and pH8 showed a broad endothermic peak between 74.29 °C-102.32 °C and 47.42 °C -106.63 °C indicating formation of complex. But DSC thermogram of drug resin complex prepared at pH10 showed a broad endothermic peak at 92.48 °C and a sharp endothermic peak at 109.75 °C indicating poor complexation.

Fig-12: Thermal analysis report of Dextromethorphan HBr API.

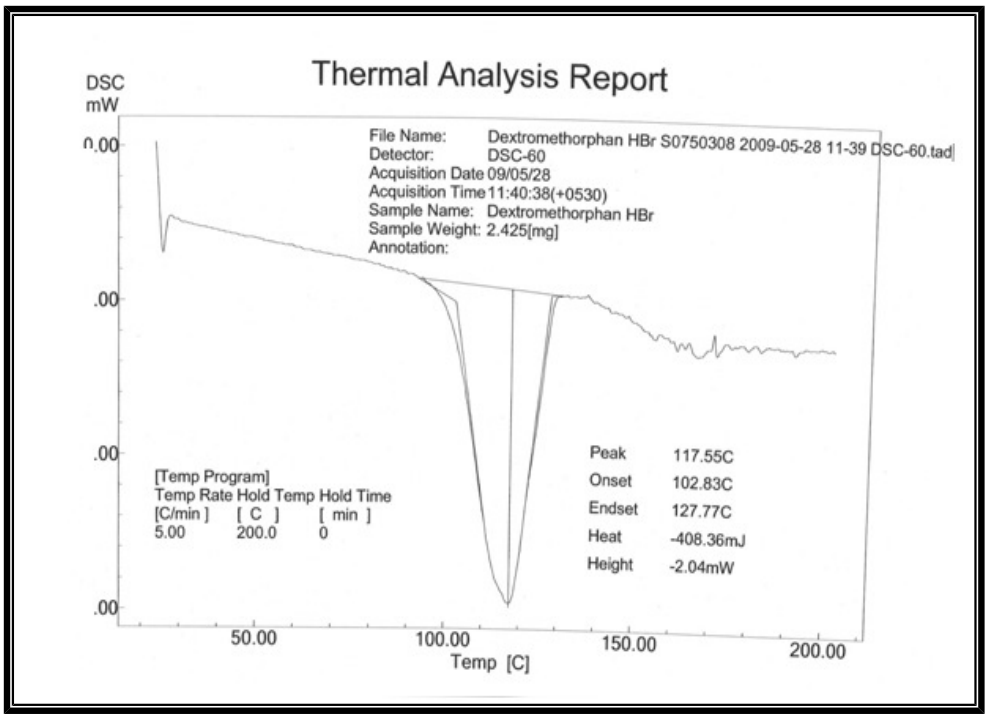


Fig-13: Thermal analysis report of Amberlite IRP64:

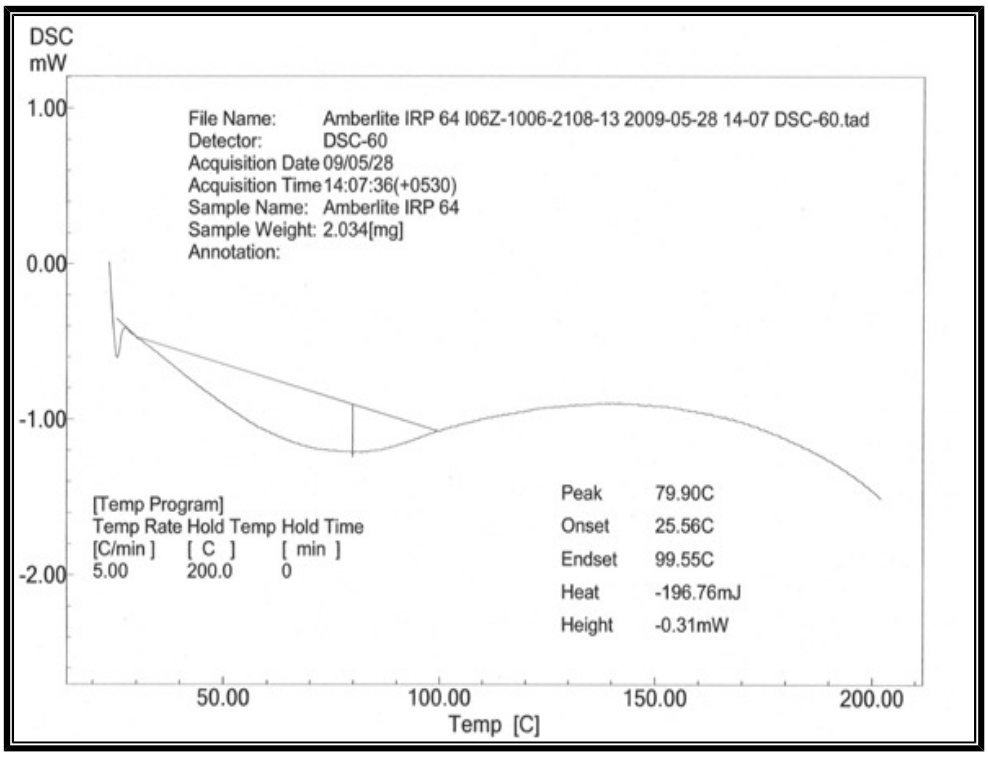


Fig-14: Thermal Analysis report of Dextromethorphan HBr- IRP64 complex at pH6

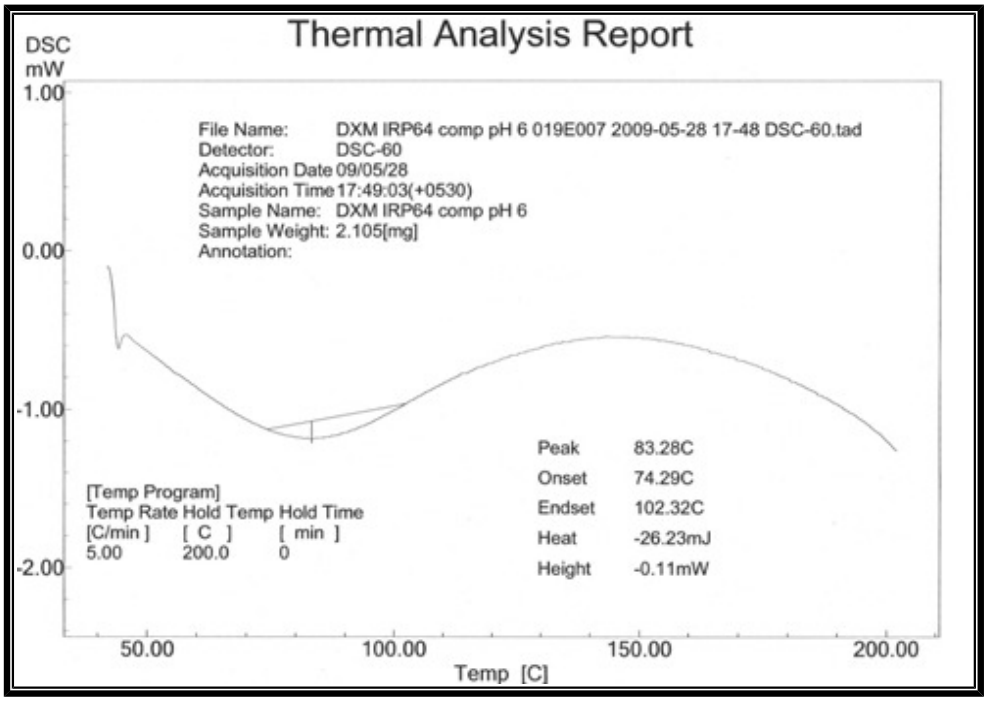


Fig-15: Thermal Analysis report of Dextromethorphan HBr-IRP64 complex at pH 8

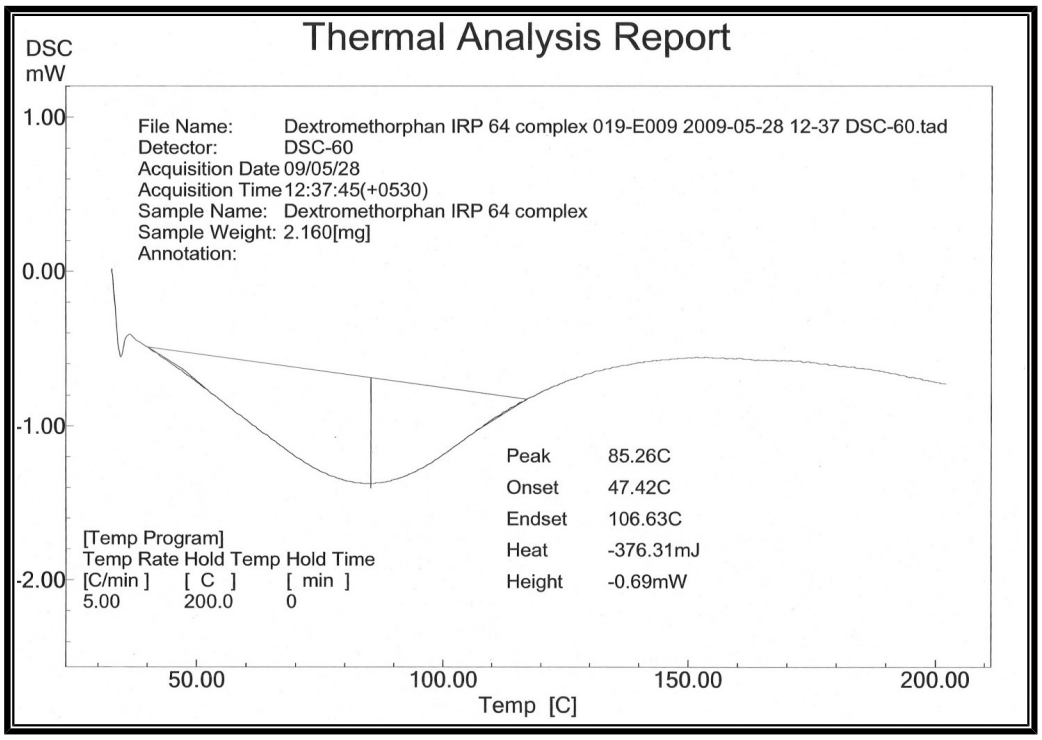
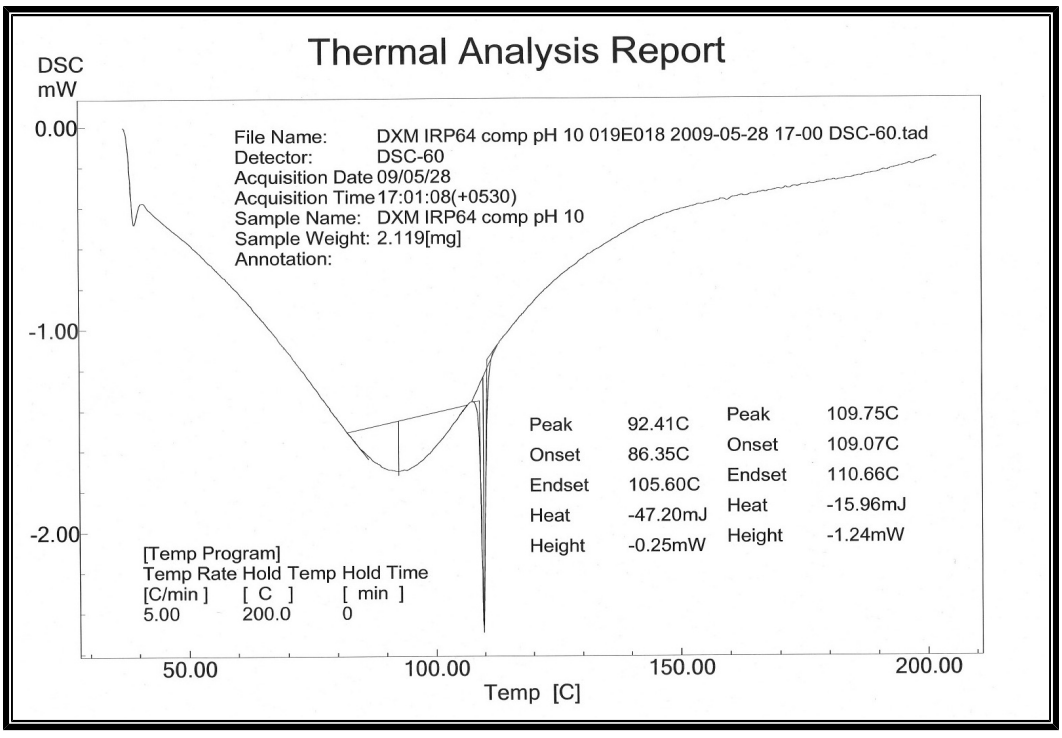


Fig-16:Thermal Analysis report of Dextromethorphan HBr-IRP64 complex at pH10



Physico-mechanical characterization of Drug resin complex:

Table-19: Particle size distribution of Dextromethorphan HBr resinate

Particle size(μ)	%w/w
420	6
250	8
177	2
149	5
<149	79

Table-20: Bulk Properties of Dextromethorphan HBr resinate

S. No	Parameters	Results
1	Bulk Density	0.47
2	Tapped Density	0.65
3	Carr's index	27
4	Hausner's Ratio	1.39
5	Angle of Repose	28.3

Result and discussion: The physico mechanical properties of the drug-resin complex such as particle size distribution, angle of repose, bulk density and tapped density, compressibility index (CI), and Hausner's Ratio were determined. The results are presented in the Table No.19 and 20 respectively.. The CI and angle of repose of drug-resin complex was found to be 27 and 28.3 indicating that the drug has poor flow properties and poor compressibility. So the diluent for the tablet formulation to be prepared by direct compression should have a granular structure with good flow property to exert a good flow of powder blent to be compressed as ODT. A suitable lubricant has to be selected to over come any manufacturing defect generally caused by poor flow of powder blend.

Drug-Excipients Compatibility Study:

Table-21: Result of Drug-Excipients Compatibility Study & Physical observation

Name of Sample	% weight Ratio	Observation	
		Polybag, 40° C/75% RH	**Glass vial,60° C**
Dextromethorphan HBr	100:0	No change observed	No change observed
Drug resin complex	100:0	No change observed	No change observed
DRC+ Mannozem EZ	50:50	No change observed	No change observed
DRC+ PharmaBurst™	30:70	No change observed	No change observed
DRC+ Crospovidone	95:5	No change observed	No change observed
DRC+ Croscarmellose Sodium	95:5	No change observed	No change observed
DRC+ Sodium starch glycolate	95:5	No change observed	No change observed
DRC+ Sucralose	99:1	No change observed	No change observed
DRC+ MAG	99:1	No change observed	No change observed
DRC+ Spearmint	95:5	No change observed	No change observed
DRC+ Magnesium Trisilicate	15:85	No change observed	No change observed
DRC+ SSF	97:3	No change observed	No change observed

Result and Discussion: After 4 weeks, the samples were visually observed. No incompatibility was found visually at 40°C/75%RH condition in both types of packs. So the selected excipients can be used for formulation of orally disintegrating tablets. The optimized amount of each excipient is to be selected by different formulation trials and the final formulation is to be prepared.

Flavor Selection: The result of the flavor selection study is shown in the table below.

Table-22: Result of Flavor Selection

Volunteers	Spearmint flavor	Cherry flavor
1	E	G
2	E	E
3	E	A
4	G	E
5	E	E
6	E	A
7	G	G
8	E	E
9	E	G
10	E	E

Discussion: Eight out of Ten volunteers rated the spearmint flavor as excellent and six out of ten volunteers rated cherry flavor as good. So mint flavor was selected for final ODT formulation.

Fig-8: Graphical representation of flavor preference of volunteers

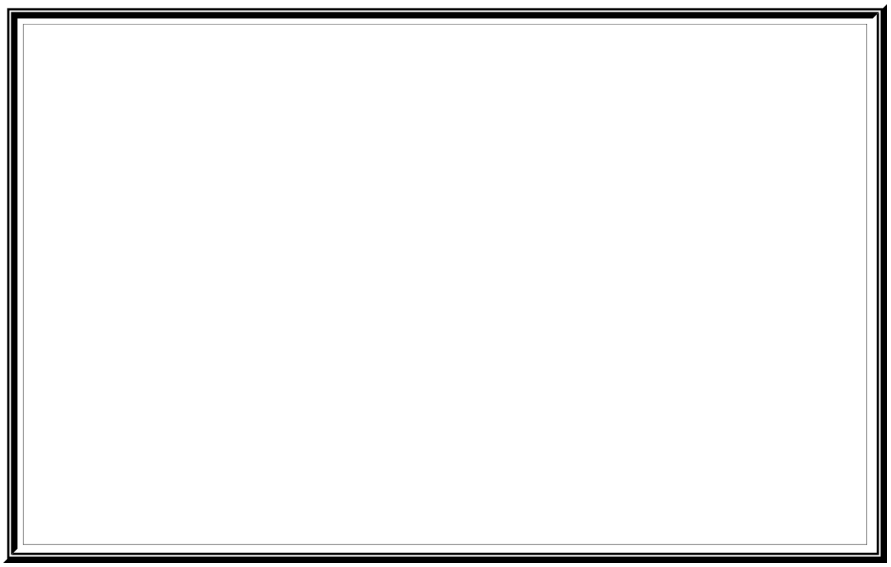


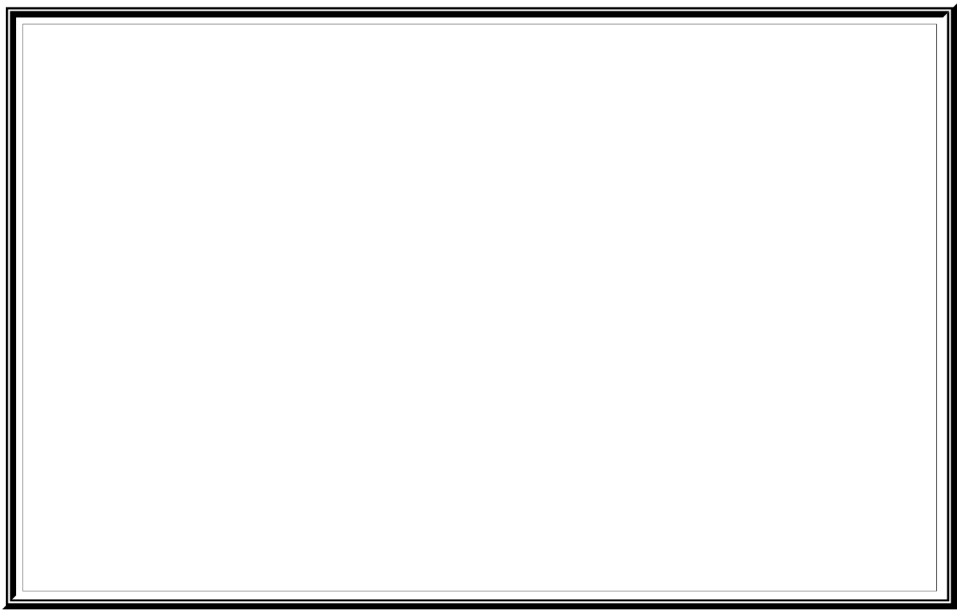
Table-23: Optimization of Flavoring Agent for Pleasant Mouth Feel:

Volunteers	0.50%	1%	1.50%
1	G	E	B

2	A	E	G
3	G	E	A
4	A	G	B
5	G	E	E
6	G	E	A
7	E	G	B
8	A	E	B
9	G	E	A
10	A	G	B

Discussion: As presented in the above table. Five out of ten volunteers selected 0.5% as good, eight out of ten volunteers selected 1% as excellent and seven out of ten volunteers rated 1.5% as bad. So the 1% concentration of mint flavor was optimized for final ODT formulation.

Fig-9: Optimization of concentration of flavoring agents



B. No	F1	F2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
Ingredients	**Quantity/ Tablet**											
DRC	43.85	43.85	43.85	43.85	-----							
D-CD complex	-----	----	----	----	110	110	110	110				
D-MTS adsorbate	----	-----	----	----	-----	-----	-----	-----	87	87	87	87
Mannogem EZ	234.55	234.55	234.55	----	168.4	168.4	168.4	-----	191.4	191.4	191.4	----
Crospovidone XL	12	-----	-----	-----	12	----	----	----	12	----	----	----
Croscarmellose Sodium	----	12	-----	-----	-----	12	----	----	----	12	----	----
Sodium Starch Glycolate	----	-----	12	-----	-----		12	----	----		12	----
Pharmaburst ™	----	----	----	246.55	----	----	----	180.4	----	----	----	203.4
Sucralose	3	3	3	3	3	3	3	3	3	3	3	3
MAG	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Spearmint Flavor	3	3	3	3	3	3	3	3	3	3	3	3
SSF	3	3	3	3	3	3	3	3	3	3	3	3

Table-24: **Formulation of Dextromethorphan HBr ODT.**

Total weight of each tablet is 300 mg.

Taken amounts of DRC, D-CD complex and D-MTS adsorbate contain 10 mg Dextromethorphan HBr.

Table-25: Evaluation of Dextromethorphan HBr ODT formulations

B. No	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Average Weight	300.48±1.01	300.66±1.12	300.34±1	300.1±0.92	299.61±1.1	299.52±1.03	299.89±0.94	300.1±1.08	300.9±1.2	299.83±1.14	300.5±1.09	301.6±101
Thickness	3.67±0.06	3.67±0.03	3.67±0.01	3.64±0.01	3.68±0.03	3.62±0.2	3.6±0.01	3.64±0.08	3.65±0.06	3.61±0.5	3.62±0.01	3.63±0.1
Diameter	9.56±0.03	9.58±0.08	9.57±0.1	9.61±0.15	9.6±0.93	9.71±0.68	9.67±0.39	9.62±0.12	9.56±0.1	9.62±0.38	9.61±0.46	9.58±0.85
Hardness	5.3±0.01	5.2±0.05	5.2±0.8	5.4±0.4	5.5±0.1	5.4±0.17	5.4±0.31	5.32±0.28	5.2±0.1	5.2±0.09	5.3±0.5	5.2±0.41
DT(sec)	22	35	42	19	30	58	70	28	21	33	38	22
%Friability	0.17	0.47	0.92	0.24	0.26	0.18	0.2	0.25	0.22	0.21	0.18	0.23
AOR	21.8	22.11	22.89	20.46	42.56	42.6	44	36.5	23.1	22.53	22.0	21.5
B.D	0.46	0.51	0.48	0.44	0.26	0.31	0.28	0.3	0.42	0.44	0.43	0.42
T.D	0.50	0.56	0.53	0.48	0.35	0.42	0.36	0.39	0.49	0.50	0.50	0.46
C.Index	8.37	8.92	9.43	8.33	25.71	26.19	22.22	23.07	14.28	12.0	14.0	8.7
H. Ratio	1.08	1.09	1.10	1.09	1.34	1.54	1.28	1.3	1.16	1.13	1.16	1.09
LOD	2.87	2.31	2.38	2.68	4.88	4.78	5.01	4.94	2.53	2.61	2.38	2.41
%Assay	101.56	103.25	102.65	102.41	98.78	101.2	100.7	99.84	104.3	101.2	100.5	102.6

Result and Discussion:

Tablets from each batch showed good uniformity of weight, thickness, diameter, ranges from 299.52 -301.6 mg, 3.61mm-3.68 mm and 9.56 mm-9.71 mm respectively. Sufficient hardness ranges from 5.2-5.4 Kp was maintained uniformly through out the different formulation batches with percent friability less than 1%.

The results of angle of repose, bulk density, tapped density, compressibility indes and Hausner ratio showed good flow property compressibility of tablet blends except batch no. from F5-F8. The unsatisfactory physico mechanical properties of these batches (F5-F8) may be due to the presence of cyclodextrin which has a poor flow and compressibility in direct compression.

Tablets containing crospovidone as superdisintegrant showed quick disintegration followed by croscarmellose sodium and sodium starch glycolate. The probable reason for delayed disintegration of the tablets with croscarmelose sodium and sodium starch glycolate might be due to their tendency form a gel like consistency. The faster disintegration of formulations containing crospovidone is due to its rapid water uptake by wicking from the medium, swelling and burst effect. Tablets containing crospovidone seems to swell immediately despite the limited swelling capacity of this class of superdisintegrants. Crospovidone exhibits a high capacity to retain deformation during postcompression. The rapid swelling of these tablets upon wetting may partly be attributed to the recovery of deformation.

Tablets containing Pharmaburst™ quick dissolving system exhibit faster disintegration than tablets containing crospovidone. This may be explained by the presence of mannitol. Prsence of higher amount of polyols increase the wetting time and subsequently disintegration time increases. As mannitol is readily soluble in water, there exists a competition between mannitol and crospovidone for water penetration into the tablets, consequently leading to poor swelling of crospovidone with subsequent delay in

Table-26: Taste evaluation of Dextromethorphan HBr ODT

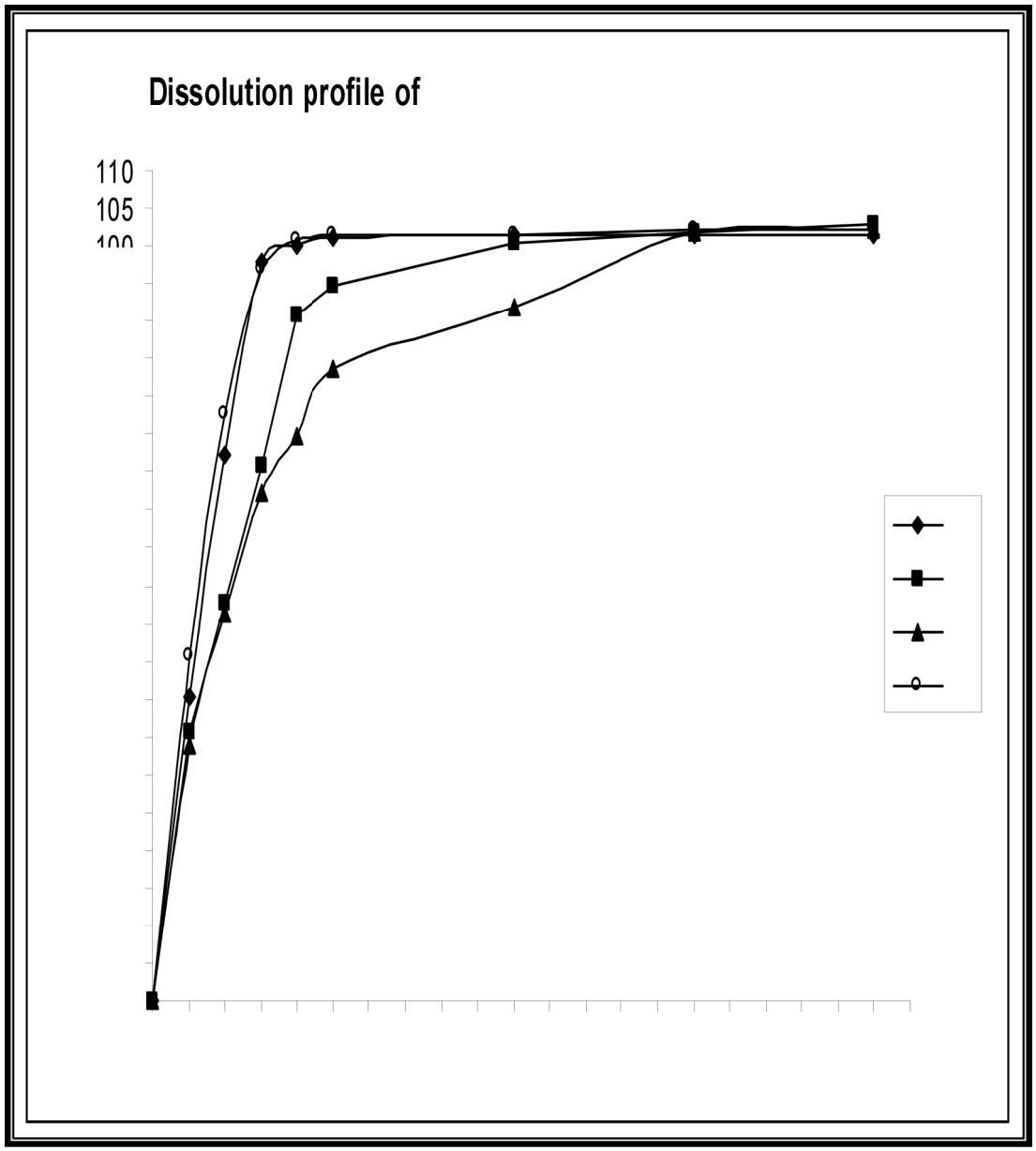
Volunteers B. No	V1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10
F1	5	5	4	5	4	5	5	5	5	5
F2	4	4	3	4	3	4	4	3	4	3
F3	4	4	3	3	3	3	4	3	3	3
F4	5	5	5	5	4	5	5	5	5	5
F5	1	1	1	1	1	1	1	1	0	1
F6	0	1	0	1	1	1	1	1	1	0
F7	1	0	1	1	0	0	1	1	0	0
F8	1	1	1	1	1	1	1	1	1	1
F9	0	0	0	1	0	0	0	0	0	0
F10	0	0	0	0	0	0	0	0	0	0
F11	0	0	0	0	0	0	0	0	0	0
F12	1	0	0	0	0	0	0	0	0	0

In-vitro Drug Release Study:

Table-27: In vitro release of Dextromethorphan HBr from ODT formulations.

Time (minutes)	F1	F2	F3	F4
0	0	0	0	0
3	40.34±0.1	35.63±0.92	33.87±1.06	45.73±0.05
6	72.16±0.34	52.58±0.14	51.22±0.92	77.52±0.02
9	97.84±0.17	70.93±0.24	67.39±0.5	96.94±0.09
12	100.09±0.2	90.68±0.2	74.66±0.64	100.91±0.1
15	101.12±0.16	94.83±0.35	83.64±0.96	101.28±0.14
30	101.29±0.31	100.52±0.72	91.84±0.83	101.59±0.21
45	101.34±0.2	101.89±0.83	101.86±0.78	102.12±0.04

Fig-11: Dissolution profile of Dextromethorphan ODT



Discussion: Formulation of B.No. F1 and F4 showed very good immediate drug release in compare to F2 and F4. More than 95% drug release was achieved with in 9 minute.

In the present work our aim was to develop such a formulation which shows less disintegration time, good taste and mouth feel and immediate drug release profile. Considering all the parameters, formulations of B.No. F1 and F4 have been found to be the best formulations with all respect.

Table-28: Final Optimized Formulation of Dextromethorphan ODT

B. No.	F1	F4
Ingredients	**Quantity/ Tablet**	
DRC	43.85	43.85
Mannitol	234.55	--
Crospovidone	12	--
Pharmaburst ™		246.55
Sucralose	3	3
MAG	0.6	0.6
Spearmint flavor	3	3
SSF	3	3

Total weight of each tablet is 300 mg.

Table-29: Inactive ingredient potency of selected excipients

Name of the excipients	Maximum allowable daily intake (mg) [CDER, US FDA- IIG Limit]
Mannitol	221.00
Crospovidone	15.00
Croscarmellose sodium	13.00
Sodium starch glycolate	71.43

STBILITY STUDY:

The finally optimized formulations of B.No. F1 and F4 were kept for stability study at 40° C/75% RH. Different physical parameters, assay and in vitro drug release study were carried out after one month. The results after one month stability period are shown in the table.

Table-35: Observations of 1 month Stability Study

Evaluation	Pack details and condition

Average Weight (mg)	300.48±1.01	300.1±0.92	300.94±1.1	300.20±1.06	300.5±1.14	300.28±1.12
Thickness (mm)	3.67±0.04	3.64±0.06	3.7±0.11	3.66±0.07	3.68±0.3	3.64±0.23
Diameter	9.56±.03	9.61±0.05	9.6±0.04	9.63±0.02	9.58±0.06	9.60±0.08
Hardness (Kp)	5.3±0.16	5.5±0.11	5.1±0.2	5.4.±0.18	5.5±0.26	5.8±0.31
Friability (%)	0.17	0.24	0.2	0.27	0.1	0.18
D. T. (sec)	22	19	20	20	22	21
Assay (%)	101.7	102.41	101.53	102.0	101.65	101.94
Taste evaluation	5	5	5	5	5	5

Each value of average weight, thickness, diameter and hardness is mean± SD

In vitro drug release study of 1 month stability sample: Samples of Dextromethorphan HBr ODT of each type of pack were withdrawn after one month and in vitro drug release study was carried out using same method used for initial samples.

Table-36: In vitro drug release after 1 month stability study

Each value is mean±SD

Fig-17: Dissolution profile of 1 month stability sample of Dextromethorphan HBr ODT

Time	% Drug release ± SD			
	F1		F4	
	PVC PVDC 60 GSM	HDPE	PVC PVDC 60 GSM	HDPE
0	0	0	0	0
3	42.84±1.24	32.22±0.1	45.14±1.2	36.37±0.4
6	75.25±1.16	70.3±0.53	77.76±0.9	72.87±0.16
9	99.52±0.9	95.3±0.63	97.17±1.1	95.47±0.25
12	100.1±1.04	99.97±0.2	100.45±0.87	100.04±0.14
15	101.28±0.22	101.07±0.42	101.72±1.16	100.43±0.11
30	101.43±0.12	101.4±0.35	101.78±1.22	100.82±0.31
45	101.5±0.54	101.43±0.15	102±1.52	101.26±0.46

Result and discussion: No observed change was found in the tablet evaluation parameters in both types of packagings. In vitro drug release study also showed no observed change when compared with the initial release.

SUMMARY AND CONCLUSION

- The present study was carried out to develop a solid oral dosage form of Dextromethorphan HBr in the form of orally disintegrating tablet having pleasant taste and mouth feel that disintegrate within few seconds upon placing on tongue.
- Since Dextromethorphan HBr is extremely bitter, different techniques of taste masking were applied to reduce bitterness of drug and to get palatable formulation. The techniques used were ion-exchange resin complexation with Amberlite IRP64, inclusion complexation using β cyclodextrin and adsorbate formation with magnesium trisilicate and ion exchange resin complexation which is simplest, efficient and cost effective is selected for further work.
- In present study, it is found that Amberllite IRP 64 can mask bitter taste of Dextromethorphan HBr by complex formation.
- Maximum drug loading is achieved using Amberlite IRP 64 and immediate drug release is achieved during dissolution study.
- DSC study shows complete complexation of Dextromethorphan- Amberlite IRP 64 complex prepared maintaining the pH of complexing medium at 8.
- Tablets prepared by direct compression are visually attractive, possess good mechanical strength with sufficient hardness.
- Targeted invitro disintegration time is achieved by using crospovidone as a superdisintegrant.
- Spray dried mannitol of SPI Pharma (Mannozem EZ) provides very good flow of the powder blend and excellent smooth mouthfeel has been experienced by volunteers. Mannitol contributes to the good taste of the formulation due to it's cooling sensation in mouth.

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